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EFFECT OF ADRENALINE, NORADRENALINE AND OCTAPRESSIN® ON BLEEDING AND CIRCULATION IN EAR OPERATIONS

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Bleeding is perhaps the most harmful factor in modern otologic micro surgery. The side effects of adrenaline are well known and therefore a study was made where Octapressin, or Octapressin and noradrenaline, was used to control bleeding at 90 ear operations. The results show that neither of the agents has the efficiency of adrenaline as far as hemostasis is concerned. Circulatory disturbances were slight when Octapressin was administered whereas adrenaline caused great changes in blood pressure and heart rate on patients under general anaesthesia. On the other hand the best bleeding control was obtained with adrenaline. The authors suggest that administration of local anaesthetic especially with adrenaline should precede induction of general anaesthesia.

Hemostasis in the operative field is of great importance during ear operations from the point of view of both the procedure itself and its successful outcome. Of the vasoconstrictors reducing capillary bleeding, adrenaline has proved the most effective one, and since 1914 it has been the vasoconstrictor most commonly used with local anaesthetics (Braun, 1914). Fairly frequently, however, the use of adrenaline has been associated with undesirable side effects, such as tachycardia, arrhythmia, increased blood pressure, nausea, giddiness and collapse. These complications may even involve hazard to life, particularly in persons with pre-existing cardiovascular disease.

With a view to increased safety of operations on the ear we have therefore studied the possibilities of replacing adrenaline wholly or in part by noradrenaline or Octapressin® Sandoz, which both have considerably weaker pharmacological effects than adrenaline.

PHARMACOLOGY

Adrenaline and noradrenaline belong to the group of so-called sympathomimetic amines, which are sympathetic stimulators. In man these occur in the adrenal medulla or at sympathetic nerve endings as impulse transmitters. According to Wood Smith & Stewart (1962) the sympathomimetic amines as a group cause some stimulation of the heart, constriction of the peripheral vessels with either

constriction or dilatation of other vessels, bronchial dilatation due to relaxation of the bronchial muscles inhibitory action on intestinal musculature, an increase in tone of sphincters, dilatation of pupils Most of these substances cause cerebral stimulation

A comparison of adrenaline with noradrenaline however, shows that these agents differ markedly in action

Adrenaline essentially controls the vital functions e g the release of glycogen from the muscles to form glucose in the blood and the blood supply to organs Noradrenaline is responsible for normal sympathetic tone in the blood vessels

In studying the circulatory effects of adrenaline it should be noted that they vary with the size of the dose Small doses raise the systolic blood pressure while the diastolic pressure falls to some extent, this latter because there is vasoconstriction of the vessels of the skin but dilatation of those of the muscles and liver, consequently the peripheral resistance decreases to about one half and thus the diastolic pressure falls At the same time adrenaline stimulates the heart the contractile force of the heart and its rate increase, the cardiac output rises and so the systolic pressure is increased Occasionally the rise in blood pressure may result in reflex cardiac slowing through stimulation of the baro receptors This is in accordance with the so called Marey law a rising blood pressure causes bradycardia and vice versa In most cases however, the direct cardiac effect of adrenaline is stronger than the factor causing bradycardia — In a few instances adrenaline may cause complete circulatory collapse as the blood pressure falls dramatically This may be due to acute cardiac failure tachycardia and perhaps to ventricular fibrillation — Large doses of adrenaline cause vasoconstriction also in the area of muscle and liver and an increase in both systolic and diastolic pressure follows Arrhythmias and ventricular fibrillation may also result from large doses The same applies to small doses if used simultaneously with other drugs which sensitize the heart for instance halogen containing anesthetic agents halothane cyclopropane methoxyflurane (Penthrane® Abbot) trichlorethylene (Mateo *et al* 1962 Hall & Norris 1958 Israel *et al* 1962) This is especially important in cases of heart disease Hypercapnia increases the danger of arrhythmia Coincidental use of local anaesthetic may to some extent protect the heart against these arrhythmias The coronary vessels expand slightly Even so an overdose of adrenaline causes anoxia of the cardiac muscle due to increased oxygen consumption of the cells to tachycardia and increased blood pressure This involves special danger in the case of heart disease When the adrenaline effect has disappeared so called after dilatation may ensue viz dilatation of the blood vessels with a resulting drop in blood pressure It has been attributed to decrease in vasomotor tone as a result of adrenaline action on the sympathetic ganglia

Noradrenaline exerts a different action on the circulation Even small doses raise both the systolic and diastolic pressure This is due to remarkable vasoconstriction in all tissues and to the increase in peripheral resistance The effect on the heart is minimal The cardiac output remains unchanged The irritability of the heart is somewhat increased but much less than with adrenaline Used in conjunction with drugs which sensitize the heart it may cause arrhythmias though this danger is considerably less than in the case of adrenaline The heart rate often slows down this is a result of the effect of the high blood pressure on the baroreceptors which cause reflex bradycardia The changes in blood

pressure and heart rate, on the basis of several studies, are greater than those caused by adrenaline, but the effect of noradrenaline on the heart itself is slighter and arrhythmias are more uncommon. Local vasoconstriction is not so effective as that produced by adrenaline, yet it is remarkable. After dilatation does not occur.—Noradrenaline may cause tissue damage and necroses because of ischemia. When using adrenaline this risk is less.

Adrenaline promotes cellular metabolism and oxygen consumption and increases the blood sugar level (Pekkarinen & Hortling, 1951, Nordqvist & Dhuner, 1961). Noradrenaline has been found to possess the same action, though some writers do not concur in this opinion.

Large doses of adrenaline stimulate the cerebral cortex and medulla, excitement, anxiety, headache, trembling and sometimes convulsions occur. The convulsions have occasionally been attributed to hypoxia, and even cerebral hemorrhages have been reported.—Noradrenaline does not affect the central nervous system. The central stimulation caused by adrenaline may be confused with the similar effect produced by local anaesthetics (Adriani, 1946).

Adrenaline and noradrenaline are rapidly absorbed in the liver and somewhat more slowly in the tissues (Lund, 1951). It is no longer possible to demonstrate adrenaline in the blood 5–10 minutes following intravenous injection of this substance (Helve & Pekkarinen, 1952).

Adrenaline and noradrenaline are the vasoconstrictors that are most commonly used in connection with local anaesthesia. The objective then is to

1. prolong the duration of anaesthesia,
2. reduce the toxic action of the anaesthetic by delaying its absorption into the circulation,
3. produce hemostasis in the operative field.

The amount of vasoconstrictors entering the blood depends upon the following factors: rate of absorption, detoxification and elimination of drug, total dose of drug, its concentration, vascularity of area of injection, speed of injection and general condition of patient.

Numerous investigators have noted that the addition of vasoconstrictors increases the toxicity of the anaesthetic instead of reducing it as would be desirable. Henn (1960) found that adrenaline increases the toxic action. Killian (1955) emphasizes the high incidence of complications from adrenaline. Nordqvist & Dhuner (1961) also state that adrenaline and noradrenaline increase complications, but if the patient is exposed *to vagal* irritation at operation, adrenaline depresses the vagal reflexes to some extent. Palva & Korkeila (1962) recommend local anaesthesia without vasoconstrictors in certain cases undergoing otolaryngological operations.

The most suitable adrenaline concentration of the anaesthetic solution is 1 : 200 000–1 : 300 000, and the total dose in adults should not exceed 0.20–0.25 mg (e.g. Moore, 1959).

Octapressin®, Sandoz, is a synthetic polypeptide hormone, a derivative of the pituitary posterior lobe hormones oxytocin and vasopressin. It was synthesized by Boissonas & Guttman (1960) at the Sandoz Laboratories. The natural vasopressin occurring in the pituitary is lysin⁸-vasopressin. When the tyrosine group marked 2 was exchanged for the phenylalanine group, this resulted in the clinically interesting substance phenylalanine² lysin⁸-vasopressin, viz. PLV 2 or Octapressin®, Sandoz (Berde *et al.* 1961).

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MATERIAL AND METHODS

Our study is based on 90 operations performed by one and the same surgeon on 90 patients 33 males and 57 females The age classification is given in Table 1

The table shows that two-thirds of the patients were in the age range 30 59 years The youngest was 7 years old the oldest 65 years with an average of 39 years

The surgical procedures were all middle ear operations Of the total, 62 were performed under local anaesthesia only, and 28 under general anaesthesia, combined with local anaesthesia The evaluation of vasoconstrictor effect was performed as a blind test Table 2 lists the composition of the nine anaesthetic agents used and the number of patients operated upon with each

Premedication was similar, irrespective of the type of anaesthesia all patients were given atropine sulphate, adults 0 1 mg per 10 kg of body weight, children 0 1 mg per 5 kg of body weight adults in addition meperidine hydrochloride (pethidine) with or without promethazine hydrochloride (Phenergan®), children pentobarbital The patients may be classified as follows according to premedication

atropine + pethidine + Phenergan	71
atropine + pethidine	15
atropine + pentobarbital	4
	= 90

The general anaesthetic agents are given in Table 3

Intermittent positive pressure breathing was used in 18 cases The anaesthesia was started in all cases with thiopentone sodium Succinyl choline as intravenous drip was the most common relaxant, in a few cases d tubocurarine The duration of the ear operations is shown in Table 4

TABLE 1 *Patients classified by age, 90 cases*

Age years	No of patients
0 9	4
10–19	10
20–29	10
30–39	24
40–49	19
50–59	17
60–69	6
	90

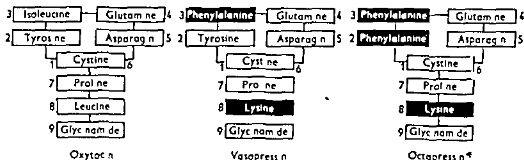


Fig. 1. The chemical compositions of oxytocin, vasopressin and Octapressin®.

All the substances in this group are characterized by their oxytocin-like effect, by their vasopressor or vasoconstrictor action, and by their antidiuretic effect (Berde *et al.* 1959, Konzett 1960, Guhl 1961). They act directly on the smooth musculature without causing sympathetic stimulation. The pharmacologic effects of the various agents differ in degree. These effects are measured and expressed in international units (IU).

Typical of Octapressin is its strong pressor or vasoconstrictor effect. It has a weak antidiuretic action and a minimal oxytocin effect.

In studying the effect on the circulation in experimental animals it appeared (Berde *et al.* 1961) that Octapressin causes increased blood pressure in the area of the systemic and pulmonary circulation, in the splanchnic area blood flow decreases, thus reducing the pressure in the portal vein. The pressure in the right auricle of the heart rises. Kidney flow is initially increased, with larger doses it decreases. The heart rate generally slows down. — Toxicity is minimal and lacks practical significance.

Guhl (1961) found that in man Octapressin causes a fivefold increase in blood pressure as compared with vasopressin, but the antidiuretic effect of the former is ten to 40 times as weak as that of the latter. Indeed this antidiuretic effect can be disregarded in practice.

Clinically, Octapressin has been used chiefly as a vasoconstrictor added instead of adrenaline to local anaesthetic agents to produce local ischemia. Studies of this question have been carried out by gynecologists, e.g. Hochuli & Kaser (1962), and by the otolaryngologists Missura & Weder (1962), De Grenus and Bollobas (1963). Adequate ischemia in the operative field has usually been achieved; most investigators, however, consider hemostasis less good than with adrenaline. Undesirable side effects have been considerably less frequent with Octapressin than with adrenaline. In some cases there has been slight increase in blood pressure and cardiac slowing, but no arrhythmias have been reported. A side effect commonly described is pallor, which is due to vasoconstriction in an extensive area and entails no danger to the patient (Klingenstrom & Westermark 1963). The preparation is suitable during different types of anaesthesia; in connection with halogen-containing anaesthetic agents it has caused no increase in irritability of the heart. According to Huggins' (1962) investigations it is very suitable as a vasopressor during general anaesthesia. Tsakiris & Buhlmann (1961) recommend it for treatment of oesophageal varices.

Bleeding was evaluated by the surgeon, the same in each case, on the basis of clinical experience according to the following scale (1) very slight, (2) slighter than usual, (3) of usual amount (4) more profuse than usual (5) extremely profuse

The chief criterion was the increased difficulty and duration of operation caused by bleeding a 'usual amount' of hemorrhage denoting that hemostasis was achieved relatively easily

DATA ON BLEEDING BLOOD PRESSURE AND HEART RATE

The variations in amount of bleeding blood pressure and heart rate are seen in Tables 5–8

TABLE 5 *Estimated amount of bleeding at 90 ear operations*

Group	Amount of bleeding	No of operations
1	Very slight	1
2	Slighter than usual	9
3	Usual amount	47
4	More profuse than usual	29
5	Extremely profuse	4
		90

TABLE 6 *Changes in systolic blood pressure after local anaesthesia at 90 ear operations*

Group	Degree of change	Rise or fall in systolic pressure mm Hg*	No of patients
1	None	< 10	6
2	Slight	10–25	36
3	Marked	30–50	30
4	Severe	> 50	18
			90

* Rise in 65 cases and fall in 19

TABLE 7 *Changes in heart rate after local anaesthesia at 90 ear operations*

Group	Degree of change	Increase or decrease in heart rate beats per minute**	No of patients
1	None	< 10	13
2	Slight	10–29	45
3	Marked	30–50	30
4	Severe	> 50	2
			90

** Increase in 49 cases and decrease in 34

TABLE 2 *The nine local anaesthetic solutions, the various vasoconstrictors added, and number of patients operated on using each solution; 90 operations*

Anaesthetic solution	Adrenaline 1:1000, ml	Octapressin® I U	Noradrenaline 1:1000, ml	2% Carbocaine®, ml	No. of patients
1	0.5			3.5	30
2	0.3	2.5		3.5	6
3	0.3	5		3.5	3
4	0.3	7.5		3.5	23
5	0.2	7.5		3.5	1
6	0.2	10		3.5	3
7	0.2	12.5		3.5	3
8	0.3	5	0.3	3.5	20
9		10		3.5	1
					90

TABLE 3 *General anaesthetic agents used at 28 ear operations*

Anaesthetic agents	No. of patients
$N_2O + O_2$ + relaxants	17
$N_2O + O_2$ + Ether	6
$N_2O + O_2$ + Halothane	1
$N_2O + O_2$ + Penthrane®	4
	28

TABLE 4 *Duration of 90 ear operations*

Duration of operations, hours	No. of operations
< 1	72
1–2	17
2–3	
> 3	1
	90

The heart rate and blood pressure were recorded (1) the day before in the ward, (2) on the operation table prior to induction of anaesthesia (3) immediately before administration of local anaesthetic, (4) immediately after local anaesthesia and continuously until blood pressure and heart rate were stabilized, and then at 10-minute intervals to the end of operation (5) in the ward two hours after completion of operation

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TABLE 9. *The various local anaesthetic solutions used and the degree and incidence of the resulting changes in heart rate and blood pressure, as well as the amount of bleeding during operation.*

	Number of patients				
	Solution 1	Solutions 2, 3	Solution 4	Solutions 5, 6, 7, 9	Solution 8
Changes in heart rate and blood pressure					
None	2	0	1	0	1
Slight	6	2	4	3	8
Marked	13	5	14	5	6
Severe	9	2	4	0	5
	30	9	23	8	20
Amount of bleeding					
Very slight	1	0	0	0	0
Slighter than usual	6	1	1	0	1
Usual amount	17	3	14	1	12
More profuse than usual	6	5	8	5	5
Extremely profuse	0	0	0	2	2
	30	9	23	8	20

TABLE 10 *The various local anaesthetic solutions used and the degree and incidence (expressed as a percentage) of resulting changes in heart rate and blood pressure, as well as the amount of bleeding during operation*

	Per cent of total number of patients in each group				
	Sol 1 (30 patients) %	Sol 2, 3 (9 patients) %	Sol 4 (23 patients) %	Sol 5, 6, 7, 9 (8 patients) %	Sol 8 (30 patients) %
Changes in blood pressure and heart rate					
None	7	0	4	0	5
Slight	20	22	17	47	40
Marked	43	56	61	63	34
Severe	30	22	17	0	5
Amount of bleeding					
Slight or usual	80	44	65	12	65
Profuse	20	56	35	88	35

Table 8 combines the changes in blood pressure and heart rate shown in Tables 6 and 7, and the circulatory changes thus obtained are divided into four groups according to degree of severity, as follows:

Group 1, no change: maximum change in heart rate and/or blood pressure less than 10 mm Hg and/or beats per minute.

Group 2, slight change: maximum change in heart rate and/or blood pressure from 10 to 29 mm Hg and/or beats per minute

Group 3, marked change: maximum change in heart rate and/or blood pressure from 30 to 50 mm Hg and/or beats per minute

Group 4, severe change: the change recorded in heart rate and/or blood pressure exceeds 50 mm Hg and/or beats per minute

TABLE 8 *Incidence of changes in heart rate and blood pressure after local anaesthesia at 90 ear operations*

Group	Degree of change	No of patients	Per cent
1	None	3	4
2	Slight	24	26
3	Marked	43	48
4	Severe	20	22
		90	

The table shows that marked circulatory changes occurred in 63 patients (70 per cent), and of this number, 20 patients (22 per cent) had severe changes (50 mm Hg and/or beats per minute or over)

The variations in amount of bleeding, blood pressure and heart rate *with different types of anaesthesia* are given in Tables 9–11 Tables 9–10 analyse these changes according to anaesthetic solution used

In Table 10 the results are expressed as percentages of the total number of patients in each group, bleeding being classified into two categories only

In Table 11 we have compared the group of patients given general plus local anaesthesia with those operated upon in only local anaesthesia with respect to the circulatory changes and amount of bleeding recorded

As already stated, severe changes in blood pressure and heart rate occurred in 20 patients of the total series, the change in six of these cases

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Amount of bleeding					
Very slight	1	0	0	0	0
Slighter than usual	6	1	1	0	1
Usual amount	17	3	14	1	12
More profuse than usual	6	5	8	5	5
Extremely profuse	0	0	0	2	2
	30	9	23	8	20

TABLE 10 *The various local anaesthetic solutions used and the degree and incidence (expressed as a percentage) of resulting changes in heart rate and blood pressure, as well as the amount of bleeding during operation*

	Per con…				
	Sol 1 (30 patients) %	%	%	%	8 …ients) %
Changes in blood pressure and heart rate					
None	7	0	4	0	5
Slight	2[illegible]	22	17	47	40
Marked	43	56	61	63	34
Severe	30	2[illegible]	17	0	5
Amount of bleeding					
Slight or usual	80	44	65	12	65
Profuse	20	56	35	88	35

amounting to 100 mm Hg and/or beats per minute The patients had been anaesthetized as follows:

Solution	patients	Local anaesthesia patients	General anaesthesia + local anaesthesia patients
1	9	5	4
2	2	1	1
4	4	2	2
8	5	2	3
Total	20	10	10

TABLE 11 *Comparison of general and local anaesthesia with respect to changes in blood pressure and heart rate and to bleeding during operation*

	General anaesthesia combined with local anaesthesia		Local anaesthesia	
	No of patients	%	No of patients	%
Changes in blood pressure and heart rate				
None	1	4	2	3
Slight	6	22	18	29
Marked	11	39	32	51
Severe	10	35	10	16
	28		62	
Amount of bleeding				
Slight or usual	23	72	34	54
Profuse	5	18	28	46

Thus, 35 per cent of those operated in general anaesthesia with assisting local anaesthesia had severe circulatory changes, whereas the corresponding figure for those operated in only local anaesthesia was 16 per cent As regards bleeding, the case is reversed good hemostasis was obtained in 72 per cent of the group receiving general and local anaesthesia but in only 54 per cent of the group of local anaesthesia alone It may be concluded, then, that general anaesthesia with added local anaesthesia was most favourable from the point of view of hemostasis even though the circulatory changes were greatest in this group

A study of the solutions used shows that solution 1 was the only one where a satisfactory result was obtained as far as bleeding is concerned bleeding of disturbing amount occurred in only 20 per cent of the cases Using solutions 4 and 8 satisfactory hemostasis was achieved in about two-thirds of the cases, but this cannot be considered sufficient It is apparent, on the other hand, that the incidence of circulatory changes was highest with solution 1 (severe changes in 30 per cent) The most dangerous changes in blood pressure and heart rate appeared when using, in addition

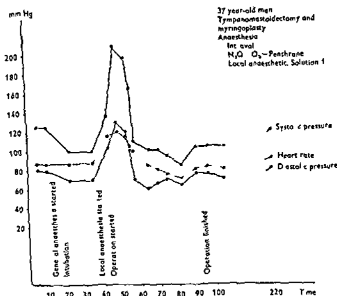


Fig 2 Typical adrenaline induced rise in blood pressure and heart rate during general anaesthesia A girl aged 14 years

to general anaesthesia solutions 1 or 8 for local anaesthesia The diagrams in Figs 2 and 3 illustrate a typical rise and fall in blood pressure caused by adrenaline solution The diagram in Fig 4 illustrates the changes in blood pressure and heart rate that we considered the most dangerous ones in our experiment

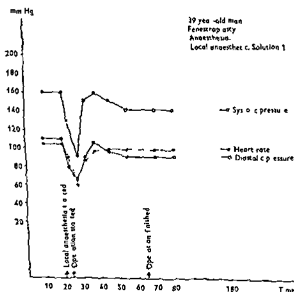


Fig 3 Typical adrenaline induced fall in blood pressure in a conscious patient A man aged 39 hypertension diagnosed earlier The drop in blood pressure was associated with slowing of heart rate simultaneously there was giddiness and sweating

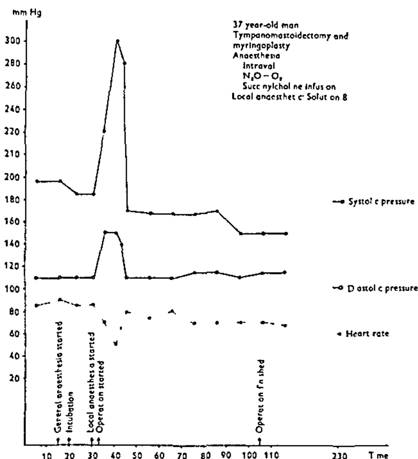


FIG. 4. Severe rise in blood pressure following administration of local anaesthesia during general anaesthesia. A man aged 37, previously healthy; preoperative blood pressure 160/90. Local anaesthesia was followed by dramatic increase in blood pressure with a simultaneous slowing of heart rate.

DISCUSSION

Choice of Anaesthetic for Ear Operations

The operations on the ear were performed in either local or general anaesthesia. The former was generally used at operations for improvement of hearing, in otosclerosis in particular, since immediate checking of the result of operation is then possible (Siirala *et al.*, 1962). Other operations on adults and all operations on children were performed under general anaesthesia. In addition to general anaesthesia, the operative field was infiltrated with a solution of local anaesthetic with added vasoconstrictor to produce better hemostasis and to make it possible to reduce the depth of anaesthesia during operation. Carbocaine®, Bofors (mepivacaine hydrochloride) was used for local anaesthesia since, even alone, it has mild vasoconstrictive properties and the added advantage of causing the least possible side-effects. In the choice of general anaesthetic we mainly followed the criteria usually associated with ear operations.

The anaesthesia should be chosen keeping in view that

1 the operative field should be ischemic as far as possible even the slightest hemorrhage obscures the view under the microscope
2 the patient should be absolutely immobile the slightest head movement sometimes even deep breathing may be disturbing or dangerous during manipulation under the microscope in the area of the middle ear particularly the fenestra ovalis
3 recovery from anaesthesia should be smooth and quiet exertion coughing and vomiting may impair the result many ear operations tend themselves to cause nausea and dizziness and as far as possible any further increase of these undesirable effects by means of the anaesthesia should be avoided
4 the surgeon should have facilities for using diathermy and vasoconstrictors for full hemostasis

We have been studying different types of anaesthesia in an attempt to find a routine method applicable to all ear operations at our hospital Operation in hypotension has thus been omitted

It is common knowledge that bleeding is more profuse at operations in general anaesthesia than in locally anaesthetized, conscious patients To understand this the effect of general anaesthesia on the hemodynamic status must be known According to Wylie & Churchill Davidson (1960) a conscious patient has a relatively slight skin and muscle flow When inducing general anaesthesia the blood vessels of the skin and muscle are dilated during the first few seconds and skin and muscle flow increases in the adult by a total of about 1750 ml This rise reaches a maximum after about 5 minutes When anaesthesia has continued 40–60 minutes the blood flow is gradually restored to its initial value The increase in skin and muscle flow is accompanied by a decrease in flow in the splanchnic area and kidneys During light anaesthesia the cardiac output initially rises During the maintenance of anaesthesia the cardiac output is reduced a change occurs in blood distribution the kidney flow particularly decreases and the same applies to skin and muscle flow However ischemia in the operative field if thus obtained by means of deep anaesthesia does not seem expedient since the other functions of the body are needlessly depressed at the same time It is the purpose of present day anaesthesia to avoid this by utilizing muscle relaxants in addition to light anaesthesia There are other ways and means available for hemostasis in the operative field

All anaesthetic agents cause depression of the myocardium (Price & Helrich 1948) In the very first stages of anaesthesia there is a transient rise in cardiac output (Prime & Gray 1952) especially in the case of ether which stimulates the secretion of adrenaline Even with ether depression sets in at a later stage Blood pressure falls as a result of myocardial depression The decrease in blood pressure common during induction and early stages of anaesthesia is a consequence of the prevailing vasodilatation using halothane this is especially remarkable Halogen containing

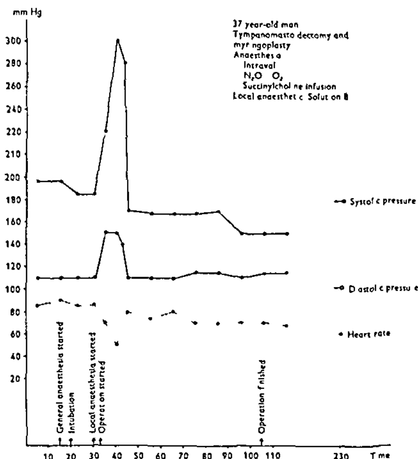


FIG 4 Severe rise in blood pressure following administration of local anaesthesia during general anaesthesia A man aged 37 previously healthy preoperative blood pressure 160/90 Local anaesthesia was followed by dramatic increase in blood pressure with a simultaneous slowing of heart rate

DISCUSSION

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TABLE 12 *Blood flows in the conscious state, under light and deep anaesthesia*

(According to Wyke and Churchill Davidson 1960)

	Conscious ml/min	Light anaesth ml/min	Deep anaesth ml/min
Skin flow	250	1000	500
Muscle flow	500	1500	750
Kidney flow	1400	900	200
Liver flow	1400	900	400
Brain flow	750	750	500
Coronary flow	400	400	400
Cardiac output	4,00	5450	2750

ether to a minimum Penthrane anaesthesia is still in the experimental stage at our hospital, so we can make no definite statement on its suitability at ear operations Up to the present time our experience with Penthrane appears quite favourable, the recovery phase was fairly smooth and bleeding relatively slight Using N_2O O_2 anaesthesia with muscle relaxants an ischemic field of operation was usually obtained, it was possible to use adrenaline and cautery for hemostasis and the recovery phase was smooth and as rapid as possible

Circulatory Disturbances Caused by Vasoconstrictors in Conscious and in Anaesthetized Patients

When studying the circulatory changes due to adrenaline and Octapressin and comparing the amount of hemorrhage it should be kept in mind that the effect of these vasoconstrictors appears most clearly and in purest form with local anaesthesia It must be remembered it is true that administration of local anaesthetic as such can cause changes in blood pressure and heart rate The blood of a patient awaiting operation has a higher than normal adrenaline content as a result of tension (Pekkarinen *et al* 1961) this may increase further at the start of operation raising the blood pressure and heart rate On the other hand administration of local anaesthetic may cause vagal stimulation and reflex fall in blood pressure and heart rate The effect of these factors however, may be considered relatively small in a conscious patient and the changes in blood pressure and pulse are almost wholly referable to the vasoconstrictors used The small dose of carbocaine presumably does not give rise to general symptoms

In the group of general anaesthesia however the effect of the general anaesthetic on the patients and the joint effect of the anaesthetic plus vasoconstrictors should be noted One explanation of the great changes in blood pressure and pulse rate in this group might be that the starting

substances, if used with adrenaline also increase myocardial irritability and the risk of spontaneous arrhythmias and ventricular fibrillation. This applies in particular to halothane and, to a lesser extent, to trichlorethylene and Penthrane. We have therefore avoided using these agents in combinations with adrenaline.

The effect of muscle relaxants on the circulation is slighter, though these have also been found to cause circulatory disturbances, notably vasodilatation, occasionally even decrease in heart rate. This applies especially to succinylcholine given as separate injection (Graf *et al.* 1963).

An excess of CO_2 and oxygen lack cause vasodilatation when acting simultaneously (Schmidt, 1950). Such hypercapnia and hypoxia result in profuse oozing in the field of operation. We avoided this by taking good care of free respiration and ventilating the patients well during anaesthesia using a CO_2 absorber. Hyperventilation may cause for instance the brain flow to decrease to one half of its normal amount (Kety & Schmidt, 1946), reducing bleeding in the operative field in accordance. Good hemostasis in patients under general anaesthesia in our experiment is presumably attributable to slight hyperventilation and resulting vasoconstrictive effect.

A rise in intrathoracic pressure should be avoided because this leads to compression of the large veins and thus again causes venostasis in the head region and increased venous bleeding in the operative field. Such a rise in pressure may be brought about for instance by an obstruction in the airways.

The part played by posture in the production of an ischemic operative field during general anaesthesia has been stressed (Enderby, 1954). In the case of conscious patients posture is not of so great consequence. By raising the operation table into the reverse Trendelenburg position the arterial pressure in the head area may be brought to fall 30–40 mm Hg in adults, while the pressure rises correspondingly in the lower extremities but remains unchanged in the arm. During halothane anaesthesia this is of special importance. The venous blood flows from the dilated vessels in the direction of gravity and hemostasis in the operative field improves.

Our search for an ideal method of anaesthesia for ear operations resulted in most cases in the choice of N_2O-O_2 anaesthesia with muscle relaxants and intermittent positive pressure breathing in adult cases. Succinylcholine as intravenous drip was mostly used for muscle relaxation and so we avoided the undesirable effects of succinylcholine on the heart. The operations were usually short, d-tubocurarine was used at long operations. For children spontaneous breathing and either ether or Penthrane anaesthesia was used. In the case of ether cautery was desisted from. The use of halothane is limited by its sensitizing effect on the heart and also by the resulting restless recovery phase, the patient often has clonic spasms in the muscles. Laryngeal spasm occurs especially after extubation. During recovery from ether anaesthesia undesirable nausea and vomiting also occur. Because of the added danger of explosion we restricted the use of

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points differ. At the time the local anaesthetic is administered a patient given general anaesthesia has just passed the induction: a strong peripheral vasodilation is present, the peripheral blood volume has increased, the blood pressure usually fallen slightly. The receptors have been stimulated (Robertson *et al.*, 1956) and also the myocardium temporarily, the cardiac output has increased. When by means of adrenaline we add to this status a powerful increase in cardiac irritability, an increase in the rate and contractile force of the heart and in cardiac output and also peripheral vasoconstriction, and when noradrenaline still adds a general vasoconstriction, the resulting changes are greater than if we start from the fairly normal status of a conscious patient.

The line of thought may also be as follows: the reaction caused by a certain agent in a patient is the sum of the effect caused by this agent and the counter-action produced by its effect. In a patient under general anaesthesia this counter-action is for some reason smaller, and thus the actual effect of the agent used is more clearly apparent. The nature of this depressed, anaesthetized mechanism of counter-action remains unclarified at the present time.

One method for avoiding these undesirable complications of vasoconstrictors during general anaesthesia would be to induce local anaesthesia while the patient is still conscious, and only then to start general anaesthesia. Because of the rapid absorption of adrenaline the amount of adrenaline immediately entering the circulation would by then be greatly reduced and general anaesthesia could be gradually induced without disturbances.

SUMMARY AND CONCLUSIONS

It was the purpose of the present work to study the possibilities of replacing adrenaline in part by Octapressin and/or noradrenaline at ear operations requiring good ischemia of the operative field. These agents, *variously combined, have been tried at 90 ear operations according to* blind test principle on both conscious and anaesthetized patients. The tests show that when diminishing the adrenaline dose from 0.5 mg to 0.3 or 0.2 mg, this reduction in adrenaline could not be effectively compensated with either the corresponding dose of noradrenaline or with 2.5–12.5 IU of Octapressin.

The dose used, 0.5 mg of adrenaline (1 : 1000) caused changes in blood pressure or heart rate as follows: in 73 per cent the degree of change was marked (exceeding 30 mm Hg and/or beats per minute), in 30 per cent or one of every three patients there was a severe change (exceeding 50 mm Hg and/or beats per minute). Six cases showed an extremely severe change. *In all these 6 cases, local anaesthetic had been used in connection* with general anaesthesia. Indeed the greatest changes in blood pressure and heart rate appeared in cases in which adrenaline had been administered

during general anaesthesia, in this group however, the result in regard to bleeding was most favourable To avoid undesirable reactions it is recommended that administration of local anaesthetic should precede induction of general anaesthesia so that there is time for the circulatory effects of adrenaline to pass over before general anaesthesia is started In the case of cardiovascular disease and in geriatric patients adrenaline should be used in lower doses or omitted In its place the writers recommend adrenaline-Octapressin solutions or Octapressin alone

ZUSAMMENFASSUNG

Der vielleicht unerwunschteste Faktor der modernen otologischen Mikrochirurgie ist die Blutung Die Nebenwirkungen des Adrenalins sind allen bekannt und deshalb wurde zur Hamostase in 90 Ohrenoperationen Octapressin oder Octapressin und Noradrenalin angewandt Die Resultate zeigen dass keines der Mittel in dieser Beziehung mit Adrenalin zu vergleichen ist Kreislaufbeschwerden waren bei Octapresin nur gering dagegen wurden bei Patienten in Allgemeinanasthesie mit zusatzlicher Lokalanasthetikum Adrenalin Infiltration des Operationgebietes grosse Schwankungen des Blutdrucks und der Herztatigkeit festgestellt Am besten wurde die Blutung mit Adrenalin kontrolliert Die Verfasser schlagen vor dass vor der Allgemeinanasthesie ein Lokalanästhetikum, das Adrenalin enthalt angewandt wird

REFERENCES

ADRIANI J., 1946 Some practical aspects of the chemistry and pharmacology of local anaesthetic drugs *Southern Med J* 39 143

BERDE B CERLETTI A and KONZETT H 1959 Symposium on Oxytocin Montevideo

BERDE, B., WEIDEMANN H., and CERLETTI A., 1961 Uber Phenylalanin Lysin Vasopressin *Helv Physiol Pharmacol Acta* 19 285

BOISSONAS, R A., and GUTTMANN ST., 1960 Synthèse d analogues de l oxytocine et de la lysine vasopressine contenant de la phenylanine ou de la tyrosine en positions 2 et 3 *Helv Chim Acta* 43 190

BOLLOBÁS B., 1963 Oto rhino laryngologische Erfahrungen mit Octapressin Wien Med Wschr 113 277

BRAUN H., 1914 *Local Anaesthesia* 3rd ed (translated by P Schields) Lea & Febiger Philadelphia

DE CREVES, E., 1963 Die Kreislaufstabilisierung *bei der Tonsillekt* mit in Lokalanasthesie (Ersatz des Adrenalins durch Octapressin) *Pract Otorhinolaryng (Basel)* 25 145

FYDERBY G E H., 1954 Postural ischaemia and blood pressure *Lancet I* 185

GRAF K., STROM G., and WAHLIN A., 1963 Circulatory effects of succinylcholine in man *Acta Anaesth Scand* Suppl 14

GUHL, U., 1961 Die antidiuretische und pressorische Wirksamkeit von Argin 8 Vasopressin Lysin 8 Vasopressin und Phenylanin 2 *lysin-8* Vasopressin beim Menschen *Schw Med Wschr* 91 798

HALL, K D., and NORRIS F H O., 1958 Fluothane sensitization of dog heart to action of Epinephrine *Anesthesiology* 19 631

Heinä, O., and Pekkarinen, A. 1952. Continuous intravenous adrenalin and noradrenalin infusion, effect on circulation and certain blood carbohydrates, lipids and phosphorus fractions in normal persons and patients with neurocirculatory asthenia. *Ann. Med. Exp. Fenn. 30*: 337.

Hess, L. 1960. Determination of the toxicological and pharmacological properties of carbocaine, lidocaine and procaine by means of simultaneous experiments. *Acta Anaesth. Scand. 4*, 125.

Hochuli, E., and Kaser, O., 1962. Octapressin als lokales Haemostaticum in der Gynäkologie und Geburtshilfe. *Triangel, 5*: 363.

Hügin, W. 1962. Die Verträglichkeit von Octapressin mit verschiedenen Narkosen. *Anaesthesist (Berlin), 11*: 185.

Israel, J. S., Criswick, V. G., and Dobkin, A. B., 1962. Effect of epinephrine on cardiac rhythm during anaesthesia with methoxyflurane (Penthrane) and trifluoroethylvinyl ether (Fluoromar). *Acta Anaesth. Scand. 6*: 7.

Kety, S. S., and Schmidt, C. F., 1946. The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men. *J. Clin. Invest. 25*: 107.

Killian, H., 1955. Drei Jahre Lokalanaesthesie ohne Adrenalin. *Deutsch. Med. Wschr., 80*: 1021.

Klingenström, P., and Westermark, 1963. Local effects of adrenaline and phenylalanyl-lysyl-vasopressin in local anaesthesia. *Acta Anaesth. Scand. 7*: 131.

Konzett, H., 1960. Pharmacology of oxytocin, vasopressin and analogues. In M. Schachter (ed.) *Polypeptides which Affect Smooth Muscles and Blood Vessels*, pp. 20–35. Pergamon Press, Oxford.

Lund, A., 1951. Elimination of adrenaline and noradrenaline from organism. *Acta Pharmacol. (Kbh.), 7*, 297.

Matteo, R., Katz, R., and Papper, Z. 1962. The injection of epinephrine during general anaesthesia with halogenated hydrocarbons and cyclopropane in men. I. Thrichlorethylene. *Anaesthesiology 23*: 360.

Missura, T., and Weder, A., 1962. Vergleichende Untersuchungen über das Verhalten des Kreislaufes bei der Tonsillektomie in LA mit vasokonstriktorischem Zusatz von Adrenalin bzw. PLV2. *Pract. Otorhinolaryng. (Basel), 24*: 249.

Moore, D. C., 1959. *Complications of Regional Anaesthesia*. Blackwell's, Oxford.

Nordqvist, P., and Dhuner, K. G., 1961. Influence of local anaesthetics with vasoconstrictors upon circulation metabolism. *Acta Anaesth. Scand. 5*: 63.

Palva, T., and Korkeila, J., 1962. Paikallispuudutuksen käytto korva-, nenä- ja kurkkutautialan toimenpiteissä. *Duodecim 78*: 190.

Pekkarinen, A., Castrén, O., Iisalo, E., Koivusalo, M., Laiho, A., Simola, P., and Thomasson, B., 1961. *Biochemistry, Pharmacology and Physiology*, p. 117. Pergamon Press, Oxford.

Pekkarinen, A., and Hortling, H., 1951. Effect of continuous intravenous infusion of adrenaline on circulation and blood chemistry. *Acta Endocr. (Kbh.), 6*: 193.

Price, H. L., and Helrich, M., 1948. The effect of cyclopropane, diethylether, nitrous oxide, thiopenthal and hydrogen ion concentration on the myocardial function of the dog heart lung preparation. *J. Pharm. Pharmacol. 115*: 206.

Prime, F. J., and Gray, T. C., 1952. The effect of certain anaesthetic and relaxant agents on circulatory dynamics. *Brit. J. Anaesth. 24*: 101.

Robertson, J. D., Swan, A. A. B., and Whitteridge, D. 1956. Effect of anaesthetics on systemic baroreceptors. *J. Physiol. (Lond.) 131*, 463.

Schmidt, C. F., 1950. *The Cerebral Circulation in Health and Diseases*. Thomas, Springfield, Ill.

Siirala, U., Tumio, J., and Sorjonen, S., 1962. Scandinavian course in stapes surgery. *Acta Otolaryng. (Stockh.), 55*, 189.

Tsakiris A., and Buhlmann A. Experimentelle Untersuchungen beim Menschen uber die Wirkung von Vasopressin auf die Lederdurchblutung und den portalen Druck *Helv Med Acta* 28 615

Wood Smith F G and Stewart H C., 1962 *Drugs in Anaesthetic Practice* Butterworths London

Wylie W D., and Churchill Davidson H C., 1960 *A Practice of Anaesthesia* p 368 Lloyd Luke London

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INTRATYMPANALE AUFZWEIGUNG DER CHORDA TYMPANI, EINE SELTENE ANATOMISCHE VERLAUFSVARIANTE

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Mitteilung einer seltenen intratympanalen Aufteilung der Chorda tympani. Ein dem Nervenstamm gleich starker Seitenast entsprang in Höhe des langen Amboßschenkels und verlief zum hinteren oberen Trommelfellquadranten, in dem er sich aufsplitterte. Kurze embryogenetische Deutung der Anomalie, die in Homologie zu den „Hautsinnesnerven" der niederen Wirbeltiere gesetzt wird.

Zwei- und Dreiteilung des Nervus facialis im Verlauf seines tympanalen oder mastoidalen Abschnittes sind bereits mehrfach beobachtet und beschrieben worden (Hawley, 1922, Botman & Jongkees, 1955, Fowler, jr.; Miehlke, 1960, Hahlbrock, 1960, Heermann, H ; Basek, 1962). Über gleichartige abnorme Aufteilungen der prae- oder posttrematischen Facialisäste konnte ich bei Durchsicht des anatomischen und otologischen Schrifttums bisher keine Angaben finden

Anläßlich einer Stapesplastik konnte ich nach Eröffnung des Mittelohres eine auffällige Teilung der Chorda tympani beobachten und, soweit es das Operationsziel zuließ, in ihrem Verlauf präparieren.

In dem Beobachtungsfall (*B*, O, Krankenblatt-Nr 1964/331/Fr) handelte es sich um eine 41jährige Patientin mit einer nur einseitigen (rechtsseitigen) Otosklerose Die Chorda tympani durchzog vom Facialisstamm und vor dessen Austritt aus dem Foramen stylomastoideum abzweigend in typischer Weise im Bogen aufwärts die Paukenhöhle, zwischen dem langen Amboßschenkel und dem Hammergriff zur Fissura petrotympanica verlaufend In Höhe des Amboßschenkels zweigte sich aber in einem Winkel von etwa 70° ein dem Hauptstamm annähernd gleichstarker Nervenanteil ab, der nach fast gestrecktem Verlauf in die Rückfläche des hinteren oberen Trommelfellanteiles einmündete und sich dort fächerförmig aufsplitterte Daß es sich hierbei nicht wie zunächst vermutet, lediglich um einen breiten Bindegewebszug handelte, bewies die vorsichtige mechanische Reizung des abzweigenden Nerventeiles, die fast augenblicklich Mißempfindungen im homolateralen Anteil der vorderen zwei Zungendrittel und — soweit die subjektiven Angaben der Patientin verläßlich sind — im Gehörgang auslösten

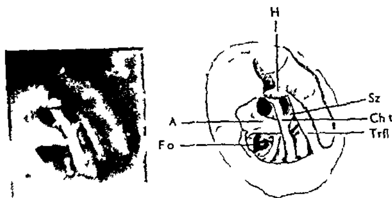


Abb. 1. Operationssitus: Aufzweigung eines dem Hauptstamm der Chorda tympani annähernd gleich starken Nervenastes in Höhe des langen Amboßschenkels. *A* Amboßschenkel, *H* Hammergriff, *Fo* Foramen ovale, *Trfl* Trommelfell, *Ch t* Chorda tympani, *Sz* Seitenzweig.

Die beschriebene Anomalie der Chorda tympani läßt sich nur aus ihrem embryologischen Verlauf zwischen der ersten und zweiten Schlundtasche und späteren Cranialwendung um die ventrale Wand der ersten Schlundtasche herum und ihren Eintritt in das Gebiet des ersten Visceralbogens verstehen (*Futamura*). Sie tritt dadurch in enge Beziehung zu den aus der vergleichenden Anatomie bei den niederen Wirbeltieren bekannten beiden Hautsinnesästen oder Seitennerven des Facialis, dem Ramus buccalis und Ramus ophthalmicus, und unterscheidet sich von diesen nur dadurch, daß sie nicht direkt aus einem besonderen Anteil des Ganglions, sondern aus dem Stamm des Nervus facialis und also erst indirekt aus der Hyoidportion des Ganglions hervorgeht (*Froriep*).

Die Chorda tympani wird dadurch aus ihrer isolierten Stellung herausgerückt. Ihr sonderbarer Verlauf unter einer Visceralspalte hindurch und in den benachbarten Bogen hinein wird verständlicher, wenn man berücksichtigt, daß außer ihr von demselben Visceralbogennerven noch zwei anscheinend gleichwertige Äste ausgehen können. Die Chorda tympani wird dadurch zum Glied eines vom Facialis ausgehenden Systems von Ästen, die in regelmäßiger Weise die 3 cranialwärts sich anschließenden Kopfglieder mit Hautsinnesorganen versorgen: die Chorda tympani den Unterkiefer, der Ramus buccalis den Oberkiefer, die Portio facialis des Ramus ophthalmicus superficialis die Orbitalregion.

Es muß bei meiner Beobachtung vorerst offen bleiben, ob eine Homologisierung mit den Verhältnissen bei den niederen Wirbeltieren und Säugetierembryonen und damit die Annahme eines entwicklungsgeschichtlichen Rückschrittes berechtigt ist, wofür die Untersuchungen von *Froriep* und von *Futamura* eine gewisse Wahrscheinlichkeit zulassen, oder ob es sich um eine unabhängig davon beim Menschen gelegentlich vorkommende anatomische Variante im Verlauf der Chorda tympani handelt. Die Be-

INTRATYMPANALE AUFZWEIGUNG DER CHORDA TYMPANI, EINE SELTENE ANATOMISCHE VERLAUFSVARIANTE

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Aus der Universitäts-Hals-Nasen-Ohrenklinik (Direktor: Prof. Dr. A. Miehlke), Göttingen

Mitteilung einer seltenen intratympanalen Aufteilung der Chorda tympani. Ein dem Nervenstamm gleich starker Seitenast entsprang in Höhe des langen Amboßschenkels und verlief zum hinteren oberen Trommelfellquadranten, in dem er sich aufsplitterte. Kurze embryogenetische Deutung der Anomalie, die in Homologie zu den „Hautsinnesnerven" der niederen Wirbeltiere gesetzt wird.

Zwei- und Dreiteilung des Nervus facialis im Verlauf seines tympanalen oder mastoidalen Abschnittes sind bereits mehrfach beobachtet und beschrieben worden (Hawley, 1922, Botman & Jongkees, 1955, Fowler, jr., Miehlke, 1960, Hahlbrock, 1960, Heermann, H., Basek, 1962). Über gleichartige abnorme Aufteilungen der prae- oder posttrematischen Facialisäste konnte ich bei Durchsicht des anatomischen und otologischen Schrifttums bisher keine Angaben finden.

Anläßlich einer Stapesplastik konnte ich nach Eröffnung des Mittelohres eine auffällige Teilung der Chorda tympani beobachten und, soweit es das Operationsziel zuließ, in ihrem Verlauf präparieren.

In dem Beobachtungsfall (*B.*, O., Krankenblatt-Nr. 1964 331/Fr.) handelte es sich um eine 41jährige Patientin mit einer nur einseitigen (rechtsseitigen) Otosklerose. Die Chorda tympani *durchzog* vom Facialisstamm und vor dessen Austritt aus dem Foramen stylomastoideum abzweigend in typischer Weise im Bogen aufwärts die Paukenhöhle, zwischen dem langen Amboßschenkel und dem Hammergriff zur Fissura petrotympanica verlaufend. In Höhe des Amboßschenkels zweigte sich aber in einem Winkel von etwa 70° ein dem Hauptstamm annähernd gleichstarker Nervenanteil ab, der nach fast gestrecktem Verlauf in die Rückfläche des hinteren oberen Trommelfellanteiles einmündete und sich dort fächerförmig aufsplitterte. Daß es sich hierbei nicht, wie zunächst vermutet, lediglich um einen breiten Bindegewebszug handelte, bewies die vorsichtige mechanische Reizung des abzweigenden Nerventeiles, die fast augenblicklich Mißempfindungen im homolateralen Anteil der vorderen zwei Zungendrittel und — soweit die subjektiven Angaben der Patientin verläßlich sind — im Gehörgang auslösten.

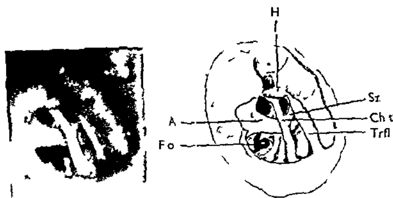


Abb. 1. Operationssituation: Abzweigung eines dem Hauptstamm der Chorda tympani annähernd gleich starken Nervenastes in Höhe des langen Amboßschenkels. *A* Amboßschenkel, *H* Hammergriff, *Fo* Foramen ovale, *Trfl* Trommelfell, *Ch t* Chorda tympani, *S* Seitenzweig.

Die beschriebene Anomalie der Chorda tympani läßt sich nur aus ihrem embryologischen Verlauf zwischen der ersten und zweiten Schlundtasche und späteren Cranialwendung um die ventrale Wand der ersten Schlundtasche herum und ihren Eintritt in das Gebiet des ersten Visceralbogens verstehen (*Futamura*). Sie tritt dadurch in enge Beziehung zu den aus der vergleichenden Anatomie bei den niederen Wirbeltieren bekannten beiden Hautsinnesästen oder Seitennerven des Facialis, dem Ramus buccalis und Ramus ophthalmicus, und unterscheidet sich von diesen nur dadurch, daß sie nicht direkt aus einem besonderen Anteil des Ganglions, sondern aus dem Stamm des Nervus facialis und also erst indirekt aus der Hyoidportion des Ganglions hervorgeht (*Froriep*).

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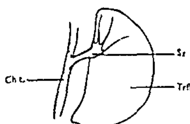


Abb. 2 Fächerförmige Aufsplitterung des Seitenastes der Chorda tympani in der Rückfläche des hinteren oberen Trommelfellanteils. *Ch t* Chorda tympani, *Trfl* Trommelfell, Sz Seitenzweig

antwortung dieser Frage werden erst weitere Beobachtungen, für die die modernen Operationsmethoden größere Möglichkeiten eröffnen, erbringen können.

SUMMARY

Report of a rare intratympanal partition of the chorda tympani. A lateral branch as strong as the nerve cord, had its source on the same level as the crus longum incudis and ran off to the superior hind quarter of the tympanic membrane in which it distributed. Short embryogenetical interpretation of this anomaly which may be related to the "Hautsinnesnerven" of the inferior vertebrates.

LITERATUR

Basek, M. 1962. Anomalies of the facial nerve in normal temporal bones. *Ann. Otol. 71*, 382.

Botman, J. W. M., and Jongkees, L. B. W., 1955. Endotemporal branching of the facial nerve. *Acta Oto-laryng. (Stockh.) 45*, 111.

Fowler, E. P. jr. zit. n. A. Miehlke.

Froriep, A. 1887. Über das Homologon der Chorda tympani bei niederen Wirbeltieren. *Anat. Anz. 2*, 486.

Futamura, R., 1906. Über die Entwicklung der Facialismuskulatur des Menschen. *Anat. Hefte 30*, 435.

Hahlbrock, K. H. 1960. Zweiteilung des N. facialis im Warzenfortsatz. *Arch. Ohr.-Nas.- Kehlk.-Heilk. 175*, 465.

Hawley, C. W. 1922. Abnormalities of the mastoid with special reference to the facial nerve. *Illinois Med. J. 41*, 130.

Hermann, H. Persönl. Mitteilung.

Miehlke, A. 1960. *Die Chirurgie des Nervus facialis*. Urban & Schwarzenberg, München-Berlin.

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Eingegangen am 28. Juli 1964

MARFAN'S SYNDROME AND HEARING ORGAN

GEORGE KELEMEN
Los Angeles California U S A

From the Los Angeles Foundation of Otology

An eleven month-old girl delivered prematurely in breech position presented multiple congenital anomalies summing up to Marfan's syndrome (arachnodactyly a mesodermal dystrophy) The most conspicuous abnormal finding in the sectional series of the right hearing organ was a bony lip that protruded from the external aperture of the vestibular aqueduct and caused considerable narrowing of this orifice It could be considered by damming up the endolymph current the cause of dilatation of the utricle and rupture of the saccular wall Marfan's syndrome is generally associated with the hearing organ only when deformities of the external ear are observed Study of the middle and the inner ear may find in these areas components of the syndrome enroling the latter among the sources of congenital deafness

During the 68 years since Marfan (1896) outlined the syndrome around arachnodactyly participation of the hearing organ has been considered to be restricted to the external ear Verse (1959) in his comprehensive survey with the subtitle Dystrophia mesodermalis type Marfan spoke of ear deformities that reached a frequency of between 25 to 70 *per cent according* to different authors Large soft auricles were found lacking *frequently* cartilaginous support together with abnormal configuration of helix anthelix crura helicis tragus antitragus Tragus and lobulus can *be absent* or the lobulus may be found abnormally large All these can be observed with the basic triad skeletal ocular and cardiovascular *changes*

Rados (1942) summarized the knowledge about Arachnodactyly *coupled* with dislocation of the lens He tabulated 204 cases with ear deformities in 35 and hearing defect in six Large auricles of unusual form lobulated or without lobules and *general deformities* figure in this enumeration Some examples will illustrate the character of *ear deformity*

Thomas (1926) found similar defects *on both sides* The crura helicis were drawn out to long folds parallel to the helix and anthelix with strongly developed antitragus *A lobulus* was absent

Ganther (1927) observed a girl seven years of age Suppuration in one

Aided by Research *Grant NB 03339 03* of the Institute of Neurological Diseases and Blindness National Institutes of Health and by a Grant from the Deafness *Research* Foundation

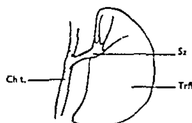


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Fowler, E. P. jr.: zit. n. A. Miehlke.

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Hahlbrock, K. H., 1960. Zweiteilung des N. facialis im Warzenfortsatz. *Arch. Ohr.-Nas.-Kehlk.-Heilk.* 175, 405.

Hawley, C. W., 1922. Abnormalities of the mastoid with special reference to the facial nerve. *Illinois Med. J.* 41, 116.

Hermann, H.: Persönl. Mitteilung.

Miehlke, A., 1960. *Die Chirurgie des Nervus facialis.* Urban & Schwarzenberg, München-Berlin.

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Fig 1 Stapedius tendon showing the complicated arrangement of its insertion Heidenhain Mallory ×

At eleven months she was dead on arrival at the hospital One week previously there were symptoms of upper respiratory infection on the morning of the death she suddenly was recognized to be severely ill with labored respiration

Autopsy followed death in two hours and revealed the following final diagnosis multiple developmental abnormalities Marfan's syndrome with small cranium right coronary synostosis arthrogryphosis (contractures) arachnodactyly osteochondrodystrophy Marfan's heart and pulmonary disease underweight brain underdevelopment and undernourishment fatty liver (?) hypoplasia of pancreatic islands Larynx considerable laxity increased mobility of the epiglottis Middle ears right tympanic membrane glistening showed a postero inferior perforation left tympanic membrane intact Bones hip entire line of epiphysis quite irregular suggesting an element of osteochondrodystrophy

Dr Sidney Farber Professor of Pathology Harvard Medical School added the following remarks to the autopsy record The majority of patients with Marfan's syndrome are not clinically diagnosed until adolescence or later this probably represents the youngest autopsied case Perhaps of sporadic type this child died probably in direct relationship to the basic disease process Of the various abnormalities which appear to be of greatest importance clinically were those found within the heart the great vessels and the lungs

ear, between $2\,^1/_2$ and 5 years resulted in a high-degree hearing loss. She was born three months premature, and the mother had suffered in the sixth month of gravidity a severe grippe.

Brock (1929) saw a patient seven years old with hearing loss; examination revealed nerve deafness with preserved caloric irritability.

Ford (1960) mentioned large ears standing away from the head (lop ears) as characteristic participants in the syndrome.

Baer & Heldrich (1963) called ear deformities "usual" and included enlarged lobes, deficiency of cartilage, overdevelopment of the crus helicis, malposition. The occasionally present deafness was, according to their opinion, incidental.

McCusick (1960) treating heritable disorders of the connective tissue said that the otologist sees the patient with the Hurler syndrome, those with osteogenesis imperfecta, and rarely those with the Marfan Syndrome.

Textbooks on otology do not mention Marfan's syndrome. Textbooks on orthopedics when treating arachnodactyly do not mention ear changes. Textbooks on medicine, pediatrics, neurology restrict themselves, in connection with Marfan's syndrome, to a few remarks on the external ear.

According to our knowledge no histological report on the ear of a Marfan patient is extant.

Case History

The girl was born by breech extraction one month prematurely, with a weight of 4 lb 11 oz. The pregnancy of the 29 year-old mother had been complicated by an auto accident in the fourth month. The family history does not mention congenital abnormalities.

At the age of six weeks she was an outpatient at the Children's Hospital Medical Center, Boston, with a diagnosis of prematurity and Marfan's syndrome, having had bilateral wrist drop at birth. Head and anterior fontanel were small, there was occipital flattening and possible synostosis of the right coronal suture. Her height consistently was one or more percentile greater than her weight even before general retardation of growth became apparent. She had loose elastic skin, low hair line, poor muscular development, prominent articular connective tissue, bilateral talipes equino valgus, bilateral dislocated hips, a light scoliosis, extension and ulnar deviation of the wrists, variable flexion limitation of elbows and knees, moderately high arched palate, long hands and gracile digits, mild microcytic anemia and, later, blue sclerae, miotic pupils, dense lenticular cores, abnormal retinal vasculature, marked myopia and bilateral esophoria (inward tending of visual lines).

At eleven weeks she was admitted for orthopedic treatment. At twenty-four weeks she was admitted a second time, this time for left perforated otitis media which healed without residua. At nine months she was admitted a third time with unexplained fever and evidence of cardiac failure. Massive cardiac enlargement involved all chambers.

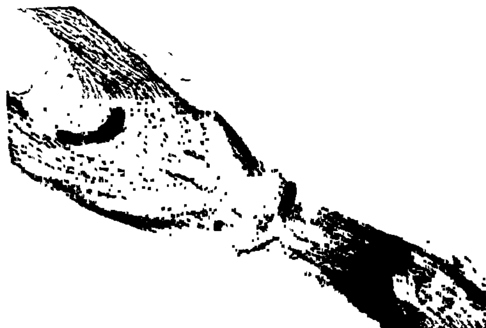


Fig. 1 Stapedius tendon, showing the complicated arrangement of its insertion Heidenhain Mallory, × 75

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FIG. 2. Normal cochlear duct, middle turn and normal density of modiolar ganglionic apparatus. Gomori impregnation, ×55.

From the right hearing organ, the inner ear was obtained, including its lateral wall with the fractured stapes, and a part of the incus. With embedding in celloidin a horizontal sectional series was prepared, stained with hematoxylin-eosin, Heidenhain-Mallory, impregnated secundum Gomori, with gold toning, while part of the sections were mounted unstained for examination in polarized light and under phase illumination.

The dura was thickened but without engorgement. Mastoid and apex were equally cancellous with pneumatic cells of approximately identical size at both locations. The footplate of the stapes was fractured, insertion of the stapedius tendon into the postero-inferior periphery of the stapes capitulum (Fig. 1) was normal. The medial fragment of the footplate was luxated towards the niche with the oval ligament here torn while the other extremity of the ligament, with the base of the lateral crus, was normal.

In the cochlea the membrane of the round window was bulging toward the scala while it straightened out in the lower sections. The niche of the round window was free. Reissner's membrane was in some of the sections retracted, in the majority straight. In the portion of the modiolus corresponding to the basal turn many spaces were empty, in contrast to the well-filled modiolar canal in the higher portions (Fig. 2). The organ of Corti was well preserved even in the basal turn opposite the empty modiolar spaces. The vene of the cochlear aqueduct was, in its canal, engorged.

The utriculo-ampullar spaces were distended (Fig. 3) and the saccular



Fig 3 Dilatation of the utriculo ampullar space Gomori impregnation × 30

wall was broken At the periphery of the canals the original relation in volume of endo and perilymph seemed to be normal Maculae and cristae were normal albeit the latter lost their cupulae

At the bottom of the opercular plate the endolymphatic duct was dilated with large polypous rugae The loose structure of the latter pointed to edematous origin some degree of cellular infiltration was present The opercular plate was drawn out into a long lip compressing the lumen of the duct considerably This lip turned out to be when followed in the sectional series a rather slender spur under the level of which the orifice regained its original width (Figs 4 5 and 6) But even farther down the intradural portion of the saccus retained the configuration into which it was forced by the stenotic portion of the opercular orifice

Comment

No deformities of the external ear were noted in the present case Lack of the tympanic membrane excluded adequate interpretation of the conditions in the middle ear as to the possible presence of residua after the otitis suffered half a year before death The stapedial fracture may or may not have been connected with the breech extraction a frequent source of birth injury

In the internal ear noteworthy findings were present in the cochlear and the vestibular portion



Fig. 4. External aperture of the vestibular aqueduct at a level above the lip shown in Fig. 5. Hematoxylin eosin, ×30.

In the *cochlea* empty modiolar spaces were observed opposite intact organ of Corti in the basal turn. This points to a possible lack of higher frequencies in later age.

In the *vestibular* apparatus conditions around the endolymphatic duct and saccus attracted attention.

Regarding the external orifice of the vestibular aqueduct, descriptions vary. Anson *et al.* (1964) called the results of related studies "conflicting". Guild (1941) explained that the BNA term "apertura externa vestibuli" was intended to designate the slit-like opening in the human, against the "slit-like" character he quoted Sterzi (1909) who proposed the term "recessus saccularis" for the enlargement of the cranial end of the aqueduct. According to Bast & Anson (1949) the opening is a fissure formed by a "depressed scale of bone", a "thin ledge of bone", compressing the duct into fan shape. Anson and collaborators called the opening a "typically slit-like" one. However, this proximal portion of the sac, i.e., the portion of the sac under the operculum, offers space for rugae to unfold. Fig. 29 in the book by Bast and Anson shows a widened lumen with high rugosities. Secretan (1944) gave an illustration of this region calling it, in this specific case, "ectasic".

In the present case the situation was an entirely different one from the usual, which is a rather abrupt tunnel-like widening at the exit with a "very capacious space" just within the aperture. Here the center portion of



Fig. 5. Osseous lip attached to the aperture. Hematoxylin-eosin. ×30.

the orifice was reduced by the lip to a narrow channel. Its influence is shown in shaping the lumen in the intradural portion of the sac (Figs. 3, 4 and 5). Behind this narrow exit in the "ectasic" portion of the canal the rugae became edematous with cellular infiltration, possibly as a consequence of blockage. The damming up of the endolymph current (plus the perilymph flow according to the concept of Anson and collaborators) may have caused the dilatation of the endolymph space in the utricle and possibly the rupture in the saccule. The mechanical obstruction would represent a severe interference with the role of the saccus to act (House 1962) as an overflow reservoir in order to maintain the delicate balance of pressure within the endolymph system. Outside the ampullar region no irregularity was present in the spacial relations of endo- and perilymph within the semicircular canals.

Evaluation of the condition under the operculum must take into consideration that the distal region of the endolymphatic sac continues to grow and to change form according to Werner (1960) up to about puberty. Bast and Anson observed "folding" to be a constant feature in fetuses, children and adults. In later years further development can take place leading to contorted systems of tubules. In this sense high polyp-like rugae may be considered as premature for the age in the reported case.

A somewhat comparable condition was described (Kelemen 1956) in a girl of three years who died of erythroblastosis fetalis. The endolymphatic spaces were distended at both sides inside and outside the opercular cover

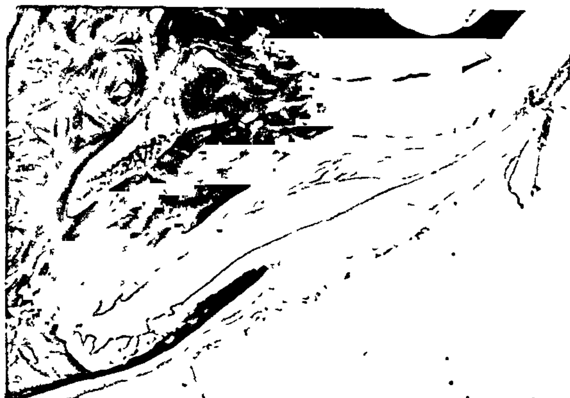


Fig. 6. External aperture below the level of the lip shown in Fig. 5. Hematoxylin-eosin. × 25.

with polyp-like, edematous and cell-infiltrated rugae. The edema was cited as characteristic of erythroblastotic changes.

Dr. Farber remarked, in connection with the autopsy record, that the current concept of the disease points to a generalized defect of the connective tissue, in which collagen and bone formation are almost equally implicated; comparable findings are seen in Morquio's disease (osteochondrodysplasia) and Toni-Fanconi disease (stunted growth with widespread deposition of cystine crystals). Nager & Meyer (1932) gave a detailed discussion on chondrodystrophy of the otic capsule, on the basis of eleven temporal bones of six cases. The disturbances of enchondral ossification described by them were not observed here but might have become rapidly conspicuous with advancing age. Asch (1960) found in achondroplasia (chondrodysplasia fetalis) irregularities of ossification, especially in the capsule of the cochlea, with normal membranous labyrinth. Arslan & Ricci (1963), in connection with their investigation on otosclerosis, postulated inclusion of some clinical conditions such as osteogenesis imperfecta, Lobstein disease, von der Hoeve disease, Recklinghausen disease, Marfan disease, *Hurler's syndrome, etc. among* the so-called collagen *diseases*. Versé, who chose the term, "dystrophia mesodermalis", reported Marfan-like conditions in RH-incompatibility and rubella embryopathy. It should not be forgotten, as Potter (1961) warned, that in some merely instances individual elements of the syndrome are present.

Via osteogenesis imperfecta the relation to otosclerosis should be recalled as described by Nager & Meyer (1932) and recently re-emphasized by Hall & Ogilvie (1961).

The blue sclerae in the present case fit into the frame of van der Hoeve's syndrome The writer's own previous observations offer several points of contact: with the presentation of Verse, erythroblastosis as mentioned above, rubella embryopathy was explored in two series of cases (Schall, Lurie & Kelemen, 1951, Kelemen & Gotlib, 1959). Pathologic conditions in the mesenchyme filling the middle and the inner ear can be added as found by the writer in several instances, e g, toxoplasmosis (Kelemen, 1958)

Finally, an item in the maternal history should be recalled; the severe grippe in the sixth month of pregnancy Reflection of a maternal viral pneumonia on the offspring was demonstrated in a case of influenza (Kelemen, 1960)

The hereditary factor in Marfan's syndrome was found by Varga (1962) on the basis of thirty cases with or without ectopia lentis to be of a recessive type McCusick (1962) declared the inheritance type to be an autosomal-dominant one.

ZUSAMMENFASSUNG

Eine weibliche Frühgeburt (11 Monate, Steisslage) wies eine Gruppe von Missbildungen auf, die das Bild Marfans Syndrom ergaben In der Schnittserie des *rechten* Gehörorgans war der auffallendste Befund *eine knöcherne Lippe entspringend von der Apertur* externa aquaeductus vestibuli, die diese Öffnung beträchtlich einengte Es konnte angenommen werden, dass diese Konfiguration durch Stauung des Endolymphstromes Erweiterung des Utriculus und Ruptur der Wand des Sacculus verursachte Marfans Syndrom und Gehörorgan werden im allgemeinen nur in Gegenwart von Missbildungen des äusseren Ohres im Zusammenhang erwähnt Fortgesetzte Untersuchungen des mittleren und inneren Ohres könnten weitere Komponente aufdecken und das Syndrom unter die Quellen der angeborenen Taubheit einreihen

REFERENCES

Anson, B J., Donaldson, J A., Warpeha, R L., and Winch, T R., 1964 Surgical anatomy of the endolymphatic sac and perilymphatic duct *Laryngoscope*, 74 480–497

Arslan, M., and Ricci, V., 1963 Histochemical investigation of oto-sclerosis with special regard to the collagen diseases *J Laryng*, 77, 365–373

Asch, J E., 1960 Pathology of the ear In *Otolaryngology* (H Schenck, ed), v I, chapt 4 1–69 W F Prior Co., Hagerstown Md

Baer R W., and Heldrich M D., 1963 Marfan's syndrome *Brennemann's Practice of Pediatrics*, v 4 chapt 26, 1–9. W F Prior Co., Hagerstown, Md

Bast, T H., and Anson, B J., 1949 *The Temporal Bone and the Ear* Charles C Thomas, Springfield, Ill

Boeck, J., 1929 Weiterer Beitrag zur Lehre von der Arachnodaktylie *Z Kinderheilk.*, 47, 702–714

Ford F. R., 1960: *Diseases of the Nervous System in Infancy, Childhood and Adolescence* (4th ed.). Charles C. Thomas, Springfield, Ill.

Ganther R., 1927: Ein Beitrag zur Arachnodaktylie. *Z. Kinderheilk.* 43, 724–730.

Guild S., 1941: Observations upon the structure and normal contents of the ductus and saccus endolymphaticus in the guinea pig (*Cavia cobaya*). *Amer. J. Anat.* 39, 1–56.

Hall S. and Ochsner R. F., 1961: Otosclerosis in osteogenesis imperfecta. *Acta Otolaryng.* (Stockh.), 53, 202–206.

House W. F., 1962: Subarachnoid shunt for drainage of endolymphatic hydrops. *Laryngoscope,* 72, 713–729.

Kelemen G., 1956: Erythroblastosis fetalis. Pathologic report on the hearing organ of a newborn. *Arch. Otolaryng.* (Chic.), 63, 392–398.

— 1958: Toxoplasmosis and congenital deafness. *Arch. Otolaryng.* (Chic.), 68, 547–561.

Kelemen G. and Gotlib B., 1959: Pathohistology of fetal ears after maternal rubella. *Laryngoscope,* 69, 385–397.

Kelemen, G., and Nesmith J. H., 1960: Viral pneumonia of the mother with hemorrhagic otitis in the fetus. *Arch. Otolaryng.* (Chic.), 72, 162–169.

Marfan A. B., 1896: Un cas de déformation congénitale des quatre membres plus prononcée aux extrémités, caractérisée par l'allongement des os avec un certain degré d'amincissement. *Bull. Mém. Soc. Méd. Hôp. Paris,* 13, 3e série, 220–221.

McCusick V. A., 1960: Heritable disorders of connective tissue (2nd ed.), chapt. 36–85. C. V. Mosby Co., St. Louis.

— 1962: The Marfan syndrome. In *Principles of Internal Medicine* (T. R. Harrison *et al.*, eds.), 4th ed., 1884–85. Blakiston Div., McGraw-Hill Book Co., New York, Toronto, London.

Nager F. R. and Meyer M., 1932: *Die Erkrankungen des Knochensystems und ihre Erscheinungen an der Innenohrkapsel des Menschen.* S. Karger, Berlin.

Potter Edith L., 1961: Pathology of the fetus and infant (2nd ed.). Year Book Publishers Inc., Chicago, Ill.

Rados A., 1942: Marfan's syndrome (arachnodactyly coupled with dislocation of the lens). *Arch. Ophthal.* (Par.), 27, 477–538.

Schall L. A., Lurie M. H. and Kelemen G., 1951: Embryonic hearing organs after maternal rubella. *Laryngoscope,* 61, 99–112.

Secretan J. P., 1944: De l'histologie normale du sac endolymphatique chez l'homme. *Acta Otolaryng.* 32, 119–163.

— 1944: Der Saccus endolymphaticus bei Entzündungsprozessen. *Pract. Otorhinolaryng.* 6, 1–27.

1944: A propos d'ectasies de l'oreille interne. *Pract. Otorhinolaryng.* 6, 281–288.

Thomas E., 1926: Arachnodaktylie mit Ohrmuscheldeformität und Schwimmhautbildung. *Münch. Med. Wschr.* 73, 890.

Varga B., 1960: Inherited type of Marfan syndrom. *Orv. Hetil.* 101, 438–443 (in Hungarian).

Verse H., 1959: Das Marfan-Syndrom (Dystrophia mesodermalis Typ Marfan, Arachnodaktylie). *Ergebn. Inn. Med. Kinderheilk.* 11, 140–205.

Werner C. F., 1960: *Das Gehörorgan der Wirbeltiere und des Menschen.* Georg Thieme, Leipzig.

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HEARING PROBLEMS IN A HOME FOR THE AGED

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From the Menorah Home and Hospital Brooklyn New York

A full time speech and hearing rehabilitation program is now in operation at the Menorah Home and Hospital To evaluate the auditory problems of the population pure tone testing has been performed on approximately one fourth of the residents Results of this study are reported and analyzed and the nature and possible etiology of presbyacusic hearing loss are considered

In 1959 a full time speech and hearing rehabilitation program was inaugurated at the Menorah Home and Hospital for the Aged and Infirm The Menorah Home is a nonprofit organization founded in 1909 and presently located in the Bushwick section of Brooklyn The present capacity of the Home is 420 Menorah s residents come primarily from the five boroughs of New York and the surrounding counties The Home accepts Jewish men and women over the age of 65 Persons with known malignancies contagious diseases and those who may cause harm to themselves or others are not accepted for admission In the Infirmary and Hospital divisions 250 chronically ill and senile patients receive total care including a special recreational program for those who are too confused and disoriented to benefit from the general program

The speech and hearing program started with the appointment of a Consulting Speech Pathologist and Audiologist whose services were donated on a volunteer basis This consultant (M H M) holds Advanced Certification in speech and hearing from the American Speech and Hearing Association Shortly after his appointment to the attending staff a position was created for a half time speech and hearing therapist (R G O) The demand for her services was so great that six months after she joined the staff her position was changed to full time status It is believed that Menorah was one of the first Homes for the Aged to make these services available on a full time basis

DESCRIPTION OF THE PROGRAM

One of the first items of technical equipment to be purchased was a pure tone audiometer An instrument was selected which could later be adapted for speech audiometric testing Part of the responsibilities of the speech

FORD F R, 1960 *Diseases of the Nervous System in Infancy Childhood and Adolescence* (4th ed) Charles C Thomas, Springfield Ill

GANTHER R., 1927 Ein Beitrag zur Arachnodaktylie *Z Kinderheilk*, 43 724-736

GUILD, S 1941 Observations upon the structure and normal contents of the ductus and saccus endolymphaticus in the guinea pig (*Cavia cobaya*) *Amer J Anat* 39 1-56

HALL, S., and OCHIVIE R I., 1961 Otosclerosis in osteogenesis imperfecta *Acta Otolaryng* (Stockh), 53 202 206

HOUSE W F 1962 Subarachnoid shunt for drainage of endolymphatic hydrops *Laryngoscope* 72 713 729

KELEMEN G., 1956 Erythroblastosis fetalis Pathologic report on the hearing organ of a newborn *Arch Otolaryng* (Chic), 63 392 398

— 1958 Toxoplasmosis and congenital deafness *Arch Otolaryng* (Chic), 68 547-561

KELEMEN G, and GOTLIB, B., 1959 Pathohistology of fetal ears after maternal rubella *Laryngoscope* 69 385 397

KELEMEN, G., and NEASHAM J H, 1960 Viral pneumonia of the mother with hemorrhagic otitis in the fetus *Arch Otolaryng* (Chic), 72, 162 169

MARFAN A B., 1896 Un cas de déformation congénitale des quatre membres plus prononcée aux extrémités caractérisée par l'allongement des os avec un certain degré d'amincissement *Bull Mem Soc Méd Hop Paris* 13 3e série 220 221

McCUSICK V A., 1960 Heritable disorders of connective tissue (2nd ed), chapt 36-85 C V Mosby Co., St Louis

— 1962 The Marfan syndrome In *Principles of Internal Medicine* (T R Harrison *et al* eds) 4th ed, 1884 85 Blakiston Div., McGraw Hill Book Co New York, Toronto London

NAGER F R., and MEYER M., 1932 *Die Erkrankungen des Knochensystems und ihre Erscheinungen an der Innenohrkapsel des Menschen* S Karger Berlin

POTTER EDITH L., 1961 Pathology of the fetus and infant (2nd ed) Year Book Publishers Inc Chicago, Ill

RADOS A, 1942 Marfan's syndrome (arachnodactyly coupled with dislocation of the lens) *Arch Ophtal* (Par) 27 477 538

SCHALL, L A LURIE M H and KELEMEN G 1951 Embryonic hearing organs after maternal rubella *Laryngoscope* 61 99 112

SECRETAN J P 1944 De l'histologie normale du sac endolymphatique chez l'homme *Acta Otolaryng* 32 119 163

— 1944 Der Saccus endolymphaticus bei Entzundungsprozessen *Pract Otorhinolaryng* 6 1 29

— 1944 A propos d'ectasies de l'oreille interne *Pract Otorhinolaryng* 6 281 288

THOMAS E., 1926 Arachnodaktylie mit Ohrmuscheldeformitat und Schwimmhautbildung *Munch Med Wschr* 73 890

VARGA B 1960 Inherited type of Marfan syndrom *Orv Hetil* 103 438 443 (in Hungarian)

VERSE H 1959 Das "Marfan Syndrom" (Dystrophia mesodermalis Typ Marfan Arachnodaktylie) *Ergebn Inn Med Kinderheilk* 11 140 205

WERNER C F 1960 *Das Gehörorgan der Wirbeltiere und des Menschen* Georg Thieme Leipzig

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TABLE 1 *Mean air conduction threshold values of each age group*

Age	125	250	500	1000	2000	4000	8000 cps
65–69 (N 12)							
Right	25	28	30	28	32	49	54
Left	23	25	28	30	34	50	60
			(P T A 30 db)				
70 79 (N 44)							
Right	31 5	32 0	35 8	39 2	47 3	64 1	70 7
Left	30 2	30 8	35 3	38 2	44 4	60 2	69 2
			(P T A 41 db)				
80 89 (N 43)							
Right	34 3	34 4	40 8	43 3	53 5	69 2	73 6
Left	37 2	38 4	44 1	47 9	53 3	70 5	74 9
			(P T A 46 db)				
90–99 (N 13)							
Right	40	38	43	49	56	69	72
Left	43	23	32	42	45	52	71
			(P T A 43 db)				

meter at the particular frequency was used in the computation of the mean threshold

Table 2 shows the mean air and bone conduction thresholds and standard deviations for residents in the 70–79 and 80–89 age groups where the largest number of subjects were found At 8000 cycles per second for air conduc-

TABLE 2 *Mean air (AC) and bone (BC) conduction thresholds and standard deviations* (S D) *for two decades*

Frequency	AC, Rt	S D	AC, Lt	S D	BC Rt	S D	BC, Lt	S D
70–79 age group								
125	31 5	13 8	30 2	14 2				
250	32 0	14 5	30 8	15 6	19 2	11 2	18 4	9 0
500	35 8	16 6	35 3	17 1	22 2	12 4	23 9	11 6
1000	39 2	16 6	38 2	18 6	31 7	11 9	32 4	12 8
2000	47 3	17 4	44 4	18 9	36 4	14 7	35 7	14 8
4000	64 1	17 7	60 2	17 7	46 4	12 1	46 4	11 8
8000	70 7	11 9	69 2	10 9				
80–89 age group								
125	34 3	15 2	37 2	17 7				
250	34 4	16 3	38 4	20 1	18 7	9.0	19 7	8 7
500	40 8	16 7	44 1	21 2	24.3	12 5	25 8	11.5
1000	43 3	16 5	47 9	21 1	37 0	11 4	37 0	12 3
2000	53 5	20 0	53 3	20 5	40 2	12 6	40 8	12 4
4000	69 2	16 8	70 5	15 8	49 5	9 5	52 6	8 7
8000	73 6	7 6	74 9	6 5				

and hearing therapist was a survey of the pure tone sensitivity of Menorah residents in order to evaluate the incidence and nature of the hearing problems requiring the attention of the newly created service. Residents with known otological and audiological problems as well as those with no known complaints were included in the survey. Prior to the hearing test an ear, nose and throat examination was performed by the attending otolaryngologist.[1] Pure tone audiograms have been performed thus far on 112 residents or approximately one fourth of the in-patient population. The present paper is devoted to a summary and evaluation of the results of this survey. Problems of audiological and speech *rehabilitation* will be covered in a series of separate papers.

It is recognized that problems of speech discrimination are highly significant in an aged population. Cawthorne (1951) among others has pointed out that it is the *intelligibility* of speech that is most affected by advancing years. The native language of most of Menorah's residents is Yiddish and a majority lack facility with English. Although standardized lists of speech audiometric materials are available in Hebrew, we have not been able to locate suitable lists in Yiddish. A project involving the preparation of appropriate lists for the determination of speech reception thresholds and discrimination scores for Yiddish speaking persons is presently under consideration.

No resident was eliminated from the study regardless of the type of loss present, its duration or the nature of the otologic findings. Thus persons with air-bone gaps of varying degrees and etiology were included in the study in contrast to most previous studies of presbycusis in which such persons are deliberately eliminated.

Testing was performed under the quietest conditions possible. Sound isolated rooms were unavailable at the time of the hearing survey. Physical calibration of the audiometer was performed at the outset and conclusion of the study and found to be within acceptable tolerances for frequency and intensity. The examiner (R. G. O.) checked her own thresholds with the audiometer at frequent intervals.

FINDINGS

The average air conduction thresholds for each age group studied are shown in Table 1. These results indicate the characteristic downward sloping audiogram characteristic of presbycusic hearing loss. The three frequency pure tone average (500, 1000 and 2000 cps) is also shown for each age group. The overall degree of hearing loss became greater as a function of age. A number of residents showed no response at the maximum of the audiometer at one or more frequencies, most frequently at 8000 cps. When this occurred, the level equivalent to the maximum output of the audio-

[1] [illegible] M.D. Presently in private practice, Toronto, [illegible]

TABLE 4 Comparison of *average air conduction thresholds with results of two other studies*

	125	250	500	1000	2000	4000	8000 cps
65–69 age group							
Miller & Ort	25	28	30	28	32	49	54
Leisti (60–69)	14	14	15	19	24	40	48
Kelley (60–69)	2	3	3	5	20	45	56
70–79 age group							
Miller & Ort	32	32	36	39	47	64	71
Leisti	18	19	23	27	31	47	59
Kelley	6	6	6	14	31	57	
80–89 age group							
Miller & Ort	34	34	41	45	53	69	74
Leisti	22	23	27	33	39	56	66
Kelley	15	13	8	8	27	60	58

were included regardless of the medical history or physical findings Leisti, in contrast, included in his investigation only persons who had never suffered from diseases which affect the middle or inner ear or from serious skull or blast injuries He further excluded all those exposed to high intensity noise environments as well as those who stated that they did not hear well although they did not know the reason why Otologic examinations were performed on 64 of Kelley's 80 subjects to insure the elimination of persons with previous pathologic changes in the ear which might account for the hearing loss present The remainder of the subjects in his series reported that, to their knowledge, they had had no previous otic disease Most other studies of hearing problems in the aged have similarly excluded persons with conductive hearing losses and histories of middle ear disease in an attempt to evaluate that loss of auditory sensitivity which is "characteristic" of the aging process Since the present survey was conducted to evaluate auditory problems in the Menorah population, we were interested in all persons in a given age group regardless of the type of loss present Furthermore, the general physical status of the Menorah resident population is poor They are, in general, persons who are unable to function independently in the community who require the constant assistance of the staff and the facilities of the Home and/or Hospital

In Table 5, the overall equality or lack of equality between the loss of hearing on the two ears in each age group is considered Category A refers to those persons whose hearing loss at a particular frequency did not differ on the 2 ears by *more than 5 db* The largest number of residents in each age group fall into this category In the 60–69 age group, 75 to 92% depending upon the frequency considered have hearing losses which can be regarded as clinically equal For the 70–79 group the per cent range is 48

TABLE 3. *Number of persons in each age group with average hearing losses on the better ear of varying degress*

Age range	15 db or less	16–30	31–60	61 db or more	Total
65–69	2	7	2	1	12
70–79	1	11	29	0	41
80–89	0	11	25	7	43
90–99	0	2	9	2	13
Total	3	31	65	10	112
Per cent	3	30	58	9	100

tion and 4000 cycles for bone conduction many residents gave no response at the maximum output of the audiometer and the mean could not be determined. If we assume that it were possible to determine the threshold at these frequencies for subjects showing no response, the resultant values would show a normal distribution. A median of the population was determined and the standard deviation based upon this median value was calculated.

Results were further analyzed to determine the number of persons in each decade with varying degrees of hearing loss. The three frequency average on the better ear was used in this analysis. Table 3 shows that relatively few residents studied have either normal hearing or a severe hearing loss. When all age groups are considered, only 3% of the residents are found to have average hearing of 15 db or better and only 9% have losses in excess of 60 db. By contrast, 88% fall within the 16–60 db range, 30% with losses between 16 and 30 db and 58% with losses between 31 and 60 db.

Results of the present survey are compared to those obtained in 2 other studies in Table 4. Our results show considerably greater hearing loss at most frequencies than either of the other studies, the differences being particularly great at the lower frequencies. The 65–69 age group, for example, shows a pure tone average loss for the 3 conversational frequencies of 30 db compared to 19 db in the Leisti (1949) study and 9 db in the Kelley (1939) study. Our 80–89 group shows an average loss of 46 db compared to 33 db in the Leisti study and 14 db in the Kelley survey.

Differences in test environment are not believed to be a highly significant factor in *accounting for the variation in results. Although Kelley performed* his tests in a "sound-proof room in the psychologic laboratories at the State University of Iowa", both the Leisti study and the present one were performed in non-sound isolated areas. Leisti had no sound proof room at his disposal and conducted his tests in a "comparatively quiet room of the hospital ward".

The main reason for the differences found appears to be the selection of subjects for each of the studies. In the present investigation, *all* persons

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The main reason for the differences found appears to be the selection of subjects for each of the studies In the present investigation, *all* persons

TABLE 6 *Frequency of occurrence of conductive components of varying degrees in each age group based upon better ear three frequency average*

Age group	10 db or less	11–30 db	31–60 db
65–69	9	3	0
70–79	36	6	[illegible]
80–89	31	8	4
90–99	11	2	0
Total	87	19	6
Per cent	78	17	5

11 to 30 db and 5% with gaps averaging 31 to 60 db Thus although conductive losses did occur the overwhelming majority of the residents tested had either no air bone gap or a difference between air and bone conduction thresholds averaging 10 db or less The more frequently encountered loss was of the sensory neural type which accounted for the greater portion of the hearing loss present Most of the residents with significant conductive components had positive findings on otological examination or histories suggestive of otosclerosis

A number of studies on presbyacusis have shown better hearing in women than in men while others have not confirmed this sex difference Bunch & Raiford (1931) were among the first investigators to note this difference They found that the auditory sensitivity of men was clearly *inferior to that* of women at 4096 cycles and above Ciocco (1932) found that the *difference in hearing* between sexes becomes apparent only after the age of 40 Leisti's *analysis of the hearing sensitivity* of 211 men and 240 women aged 16–92 years showed that by the age of 20 to 30 the hearing of men is *poorer than* that of women at 4096 and 8192 cycles He does not consider the *differences* to be conclusive and attributes them largely to the effects of noise and blast injuries on the hearing of males Pestalozza & *Shore* (1955) in a *detailed* audiologic appraisal of 185 patients ranging in age from 60 to 90 *found that sex differences* were not very important Kelley in his study of 88 adults from 50–86 years of age found no *significant differences* in hearing between men and women More recently *Klotz & Kilbane* (1962) in their report on the audiologic assessment of 100 women and 70 men between the ages of 51 and 92 *found that* above the age of 60 men have a greater hearing loss than women for *frequencies* above *1000* cps and after the age of 80 in the lower frequencies as well

The results of the present investigation were analyzed to determine whether a difference in auditory sensitivity *between* the sexes was present This analysis was performed only *for the two middle* decades where the largest number of subjects was available Results are summarized in Table 7 In the 70–79 age group average *thresholds* are slightly poorer for the women at frequencies below 4000 *cps* *This* trend is reversed at 4000 and

TABLE 5. *Degree of equality between the hearing loss on the two ears of three age groups.*

Category[a]	125	250	500	1000	2000	4000	8000 cps
65–69 age group							
A	10	10	11	10	9	9	9
B	2	2	1	1	0	2	1
C	0	0	0	1	3	1	2
70–79 age group							
A	25	24	29	26	21	28	23
B	12	10	7	9	13	11	13
C	7	10	8	9	10	5	8
80–89 age group							
A	23	26	23	23	22	23	29
B	8	6	10	8	10	9	6
C	12	11	10	12	11	11	8

[a] Category A. Right ear equal to or within 5 db of left.
Category B. Right ear poorer than left by over 5 db.
Category C. Right ear better than left by over 5 db.

to 66% and for the 80–89 group, the range is 51–67%. The frequently reported statement that presbyacusic hearing loss affects both ears equally is supported by our findings.

Audiometric studies of hearing problems in the aged indicate that presbyacusis is primarily a sensory neural hearing loss. Other studies, however, have suggested that a conductive component constitutes a significant portion of the hearing loss. Low frequency conductive losses in aged persons have been attributed by some to flaccidity of the tympanic membrane. Glorig & Davis (1961) reported studies of a group of presbyacusic subjects in whom a considerable conductive component in the *high* frequencies was present. At a recent Medical Audiology Workshop (1962) Glorig reported that the hearing loss *characteristic* of presbyacusis is a high frequency *conductive* loss. He suggested that these impairments may be the result of a loss of elasticity of the eardrum and middle ear joints accompanying the aging process. A special bone conduction vibrator not presently available to the clinical audiologist was used in his tests and bone conduction thresholds were established by Bekesy audiometry.

Glorig has emphasized the importance of *not* excluding persons with air-bone gaps in studying hearing loss in the aged. In our investigation, as previously noted, such persons were included. Table 6 shows how often a conductive loss was encountered. Eighty-seven persons or 78% of the total sample showed an average air bone gap for the three central frequencies on the better ear of 10 db or less. Only 22% of the population showed conductive losses in excess of this amount, 17% having air-bone gaps averaging

presence of a relatively mild sensitivity loss Pestalozza & Shore, for example, found that discrimination in young people was always 9-20% better than that of the old people with the same amount of hearing loss Klotz & Kilbane found in their sample that discrimination loss is much greater than would be expected on the basis of either pure tone audiometry or speech reception thresholds, especially after the age of 60 Gaeth (1948) has termed this phenomenon "phonemic regression" It is a frequent accompaniment of presbyacusic hearing loss The phenomenon probably reflects a generalized deterioration of centers within the central nervous system concerned with sound transmission and reception Such deterioration can exist in the presence of a relatively intact end organ Jerger (1960) believes that pure tone sensitivity is maximally affected by *peripheral* lesions and progressively less as the site of the lesion moves centrally Discrimination for ordinary speech is affected most by the bottle-neck region of the eighth nerve and brain stem less by cochlear lesions and not at all by a middle ear or cortical lesion

Fieandt & Saxen (1937) describe senile atrophy of the ganglion cells as an independent and self contained phenomenon where the alterations, i e atrophy of the ganglion cells and of the nerve fibers affect chiefly the proximal parts of the cochlea The Organ of Corti and the blood vessels are usually not included in the process These investigators believe that although presbyacusis may have its origin in lesions which develop on an arteriosclerotic basis in the central acoustic pathways and centers, such *lesions* are seldom the only reason for the hearing defect since *in most cases they* are also combined with a senile atrophy of the spiral ganglion cells and of the nerve fibers In a *later report*, Saxen (1952) emphasized, on the basis of 33 *histological sections*, that angiosclerotic degeneration of the *inner ear is not the main* causative factor in presbyacusis Atrophy was most noticeable *in the* vestibular portion of the spiral canal up to the region *corresponding* to the basal coil Riesco & MacClure (1948) believes that cochlear alterations occurring *with old age* are not due to vascular changes but *result from* a degenerative and atrophic neuritis Schuknecht (1955) described *an* epithelial and neural type of *presbyacusis* on the basis of the histological *findings* in several animals and 1 human *In* presbyacusis due to epithelial atrophy, the principal features of the *pathology* were atrophic degenerative changes in the membranous cochlear *labyrinth* including afferent nerve fibers which begin at *the basal end* and proceeded toward the apex Presbyacusis due to neural *atrophy is believed* to involve a decrease in population of the neurons of the auditory *nervous* pathways A third type of pathology involves neuron loss in the *higher* auditory centers, a process which Schuknecht *believes develops* independently of cerebral arteriosclerosis but may co-exist with varying degrees of it The clinical manifestations include senile *dementia* characterized by a gradual diminution of physical and mental capacity, an exaggeration of prior personality traits increasing intellectual failure, impairment of memory errors of judgment

TABLE 7 *Average air conduction thresholds for right ears of male and female residents*

	125	250	500	1000	2000	4000	8000 cps
70–79 age group							
Male (N = 20)	30	30	34	39	50	69	76
Female (N = 24)	33	34	38	40	61	60	67
80–89 age group							
Male (N = 23)	35	36	42	45	57	75	77
Female (N = 20)	33	32	40	41	50	63	70

8000 cps where the males show greater hearing loss than the females by 9 db. These results were affected by one female resident with total deafness within audiometric limits on her right ear and by two other women with profound losses present on the right ear since childhood. In the 80–89 decade, average thresholds for the males are poorer at every frequency but the differences are most marked at 2000 cps and above. Observation of the audiometric data and case histories suggest that the greater hearing loss in the males is associated with prior noise exposure associated with employment or military service. If it were possible to extract this portion of the hearing loss from the audiograms, the presbyacusic loss would probably be essentially equal for the two sexes.

The Nature of Presbyacusic Hearing Loss

A survey of the literature on hearing problems of the aged reveals considerable difference of opinion as to the nature and etiology of the "characteristic" impairment. Differences of opinion even exist on the spelling of the term "presbyacusis". It is variously spelled "presbyscusis" (Davis, *1947*), "presbyacusis" (Davis & Silverman, 1960), "presbycusis" (Kelley) and, especially in the non-American literature, "presbyacousis". There is equal disagreement on other, more significant, aspects of the condition.

Hoople (1960) believes that in evaluating geriatric hearing problems, aging is less important than accumulative ear insults. The geriatric patient brings to old age all of the otic diseases of a lifetime. The cumulative effect of these conditions clearly constitutes an important component of the total hearing picture. In planning for the rehabilitative needs of the aged hard of hearing person, all aspects of the condition must be considered. However, in assessing that segment of the hearing loss characteristic of the aging process, conductive losses due to middle ear disease must be excluded.

Most of the histological and clinical data suggest a *retrocochlear rather* than a peripheral basis for presbyacusic hearing loss. Speech audiometric studies have shown an inordinately severe discrimination problem in the

presence of a relatively mild sensitivity loss Pestalozza & Shore, for example found that discrimination in young people was always 9–20% better than that of the old people with the same amount of hearing loss Klotz & Kilbane found in their sample that discrimination loss is much greater than would be expected on the basis of either pure tone audiometry or speech reception thresholds especially after the age of 60 Gaeth (1948) has termed this phenomenon *phonemic regression* *It is a frequent accompaniment* of presbyacusic hearing loss The phenomenon probably reflects a generalized deterioration of centers within the central nervous system concerned with sound transmission and reception Such deterioration can exist in the presence of a relatively intact end organ Jerger (1960) believes that pure tone sensitivity is maximally affected by peripheral lesions and progressively less as the site of the lesion moves centrally Discrimination for ordinary speech is affected most by the bottle-neck region of the eighth nerve and brain stem less by cochlear lesions and not at all by a middle ear or cortical lesion

Fieandt & Saxen (1937) describe senile atrophy of the ganglion cells as an independent and self contained phenomenon where the alterations i e atrophy of the ganglion cells and of the nerve fibers affect chiefly the proximal parts of the cochlea The Organ of Corti and the blood vessels are usually not included in the process These investigators believe that although presbyacusis may have its *origin* in lesions which develop on an arteriosclerotic basis in the central acoustic pathways and centers such lesions are seldom the only reason for the hearing defect since *in most cases they* are also combined with a senile atrophy of the spiral ganglion cells and of *the* nerve fibers In a later report Saxen (1952) emphasized on the basis of 33 histological sections that angiosclerotic degeneration of the *inner ear* is *not* the main causative factor in presbyacusis Atrophy was most noticeable in *the* vestibular portion of the spiral canal up to the region corresponding to the basal coil Riesco & MacClure (1948) believes that cochlear alterations occurring with old *age are* not due to vascular changes but *result from* a degenerative and atrophic neuritis Schuknecht (1955) described an epithelial and neural type of presbyacusis on the basis of the histological findings in several animals and 1 human *In presbyacusis due to* epithelial atrophy the principal features of the pathology *were atrophic* degenerative changes in the membranous cochlear labyrinth including afferent nerve fibers which began at the basal end and proceeded toward the apex *Presbyacusis due to* neural atrophy is believed to involve a decrease in population *of the neurons* of the auditory nervous *pathways* *A* third type of pathology involves neuron loss in the higher *auditory centers* a process which Schuknecht believes develops independently of cerebral arteriosclerosis but *may co exist* with varying *degrees of it* The clinical manifestations include senile dementia characterized by a gradual diminution of physical and mental capacity an *exaggeration of prior personality traits* increasing intellectual failure impairment of memory errors of *judgment*

and insomnia. Presbyacusic hearing loss is characterized, Schuknecht believes, by the *absence* of the recruitment phenomenon

Sercer & Krmpotic (1958) in a study of 120 temporal bones from the sixth fetal month to the 85th year of life found that with advancing age, hyperostotic deposits develop at the fundus of the internal auditory meatus at the same time as on the inner surface of other cranial bones, which process narrows the remaining openings of the tractus spiralis foraminosus and thus exerts a continuous pressure on the nerve twigs running through it. They regard the atrophy of the nerve fibers as the primary result of this process and the degeneration of the spiral ganglion as secondary. Senile hyperostosis (overgrowth of bone due to age) is regarded as the primary cause of "pure idiopathic presbyacousis". It is considered only one of the phenomena of a general physiological process termed by the authors "hyperostosis senilis progressiva meatus acustici interni".

Jorgensen (1961) investigated changes associated with the aging process in 25 temporal bones from patients ranging in age from 2 months to 85 years. Apart from the well established loss of ganglion cells in the basal portion of the cochlea, the author demonstrated thickening of the capillary walls in the stria vascularis. This condition progresses with age and is associated with arteriosclerosis. It corresponds to the description of angiosclerotic inner ear degeneration reported by Fieandt & Saxen. These are a few of the numerous histological reports on presbyacusic hearing loss found in the literature. It appears that the hearing loss accompanying the aging process can affect any of a number of structures in the auditory system. However, degeneration of spiral ganglion cells appears to be the type of pathology most often found in presbyacusic patients.

Although arteriosclerotic and angiosclerotic changes in the inner ear have been emphasized by a number of investigators as being significantly associated with presbyacusis, clinical studies have not confirmed this relationship. Bunch (1929, 1931) found that the average hearing loss in patients with arteriosclerosis, hypertension, chronic cardiac conditions, syphilis and malignant conditions was *not* greater than the hearing loss in groups of individuals of the same age in good general health. Klotz & Kilbane in an analysis of the case histories of their subjects found that *none* of the following items occurred significantly more often in presbyacusic patients: dizzy spells, headaches, employment in a noisy place, exposure to acoustic trauma, head injury, serious disease, other ear, nose and throat symptoms, changes in sense of taste or smell or family history of high blood pressure or of deafness. The answer to one question was significantly related to degree of hearing loss. The majority of persons with good hearing said that they had had a tonsillectomy and adenoidectomy whereas those with poorer hearing said they had not. Since these authors consider presbyacusis as a sensory neural and not a conductive loss, they explained this finding as a statistical accident.

Del Giudice & Amorelli (1960) believe that one of the pathogenic elements

of presbyacusis is arteriosclerosis which is often associated with hypercholestemia A group of 10 presbyacusic subjects was administered a mixture of polyunsaturated essential fatty acids as a hypocholestemic and another group of 10 presbyacusics served as a control These investigators conclude that polyunsaturated essential fatty acids, by reducing serum cholesterol levels show an action which delays the evolution of presbyacusis when senile changes have not occurred

It is hoped that the reader will not conclude from these references that an effective way to prevent the occurrence of presbyacusis is to have a tonsillectomy and adenoidectomy and to partake of a diet high in polyunsaturated fatty acids More important it would seem, is to select ancestors who lived to a ripe old age and preserved their hearing since there appears to be a tendency for presbyacusis to occur earlier and with greater severity in some families than in others

Menorah residents whose hearing was tested showed a high incidence of arteriosclerosis diabetes, hypertension etc However, an equally large number of Menorah residents of the same age groups not included in the sample for a variety of reasons also showed a high incidence of these conditions Arteriosclerotic changes are characteristic of the Menorah population in general and the severity of these conditions does not appear to be related to the degree of presbyacusic hearing loss present

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ZUSAMMENFASSUNG

Ein vollstandiges Sprach und Gehor Rehabilitationsprogramm wird jetzt im Menorah Home and Hospital durchgefuhrt Um die Gehorprobleme der Bevolkerung feststellen zu konnen sind Gehorteste mit reinen Tonen bei ungefahr einem Viertel der Patienten vorgenommen worden Die Ergebnisse dieser Untersuchung werden dargelegt und analysiert und die Art und denkbare Atiologie der Altersschwerhorigkeit werden erortert

Die statistische Behandlung der Untersuchungsdata wurde von Herbert Rich Medizinischer Statistiker ausgefuhrt

Die Verfasser sprechen Herrn Max Wiseman Administrator Menorah Home and Hospital ihren aufrichtigen Dank fur seine stete Hilfe und Anregungen aus ohne die diese Arbeit nicht hatte durchgefuhrt werden konnen Es ist grossten

teils seinen Anstrengungen zu verdanken, dass das Programm für Sprach und Gehörrehabilitation ins Werk gesetzt und zu seinem gegenwärtigen Umfang erweitert werden konnte

REFERENCES

BUNCH C C, 1929 Age variations in auditory acuity *Arch Otolaryng* (Chic), 9 625
— 1931 Further observations on age variations in auditory acuity *Arch Otolaryng* (Chic), *13* 170
BUNCH C C, and RAIFORD T S, 1931 Race and sex variations in auditory acuity *Arch Otolaryng* (Chic) *13*, 423
CAWTHORNE T, 1951 Hearing and deafness *Acta Otolaryng* (Stockh), *40* 257
CIOCCO A, 1932 Observations on the hearing of 1980 individuals *Laryngoscope* *42* 837
DAVIS H (ed), 1947 *Hearing and Deafness a Guide for Laymen* Rinehart and Co, Inc, New York
DAVIS H (ed) and SILVERMAN S R (coed), 1960 *Hearing and Deafness* (revised edition) Holt Rinehart and Winston Inc, New York
EIFANDT H VON, and SAXEN, A, 1937 Pathologie und Klinik der Altersschwerhorigkeit *Acta Otolaryng* (Stockh) Suppl *23*
GAETH J D A study of phonemic regression in relation to hearing loss Doctoral Dissertation Northwestern University XVI 1948
GLORIG A and DAVIS H, 1961 Age noise and hearing loss *Am Otol Rhinol and Laryngol* *70* 556
DEL GIUDICE M, and AMORELLI A, 1960 Colesterolemia and presbyacusis *Arch Ital Otol* *68* 175
HOOLIE G D, 1960 Care of hearing in the elderly *Geriatrics* *15* 106
JERGER J F, 1960 Audiological manifestations of lesions in the auditory nervous system *Laryngoscope* *70* 417
JORGENSEN M B, 1961 Changes of aging in the inner ear *Arch Otolaryng* (Chic) *74* 164
KELLEY N H, 1939 A study in presbyacusis auditory loss with increasing age and its effect on perception of music and speech *Arch Otolaryng* (Chic) *29* 506
KLOTZ R E and KILBANE M, 1962 Hearing in an aging population preliminary report *New Engl J Med* *266* 277
LIISTE T I 1949 Audiometric studies of presbyacusis *Acta Otolaryng* (Stockh) *38* 555
Medical Audiology Workshop Sponsored by the Div of Otolaryngology of the University of Colorado School of Medicine Estes Park Colorado July 30 August 3 1962
PESTALOZZA G and SHORE I 1955 Clinical evaluation of presbyacusis on the basis of different tests of auditory function *Laryngoscope* *65* 1136
RUSCO MACCULLI J S 1948 Vascular disturbances of the internal ear (cochlear branch) *Rev Bras Otorinolaring* 8 3
SAXEN H 1952 Inner ear in presbyacusis *Acta Otolaryng* (Stockh) *41* 213
SCHUKNECHT H F 1955 Presbyacusis *Laryngoscope* *65* 402
SENGER A and KRMLOTI I 1958 Über die Ursache der progressiven Altersschwerhorigkeit (presbyacusis) *Acta Otolaryng* (Stockh) Suppl *143* 6

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EFFECTS OF "DOUBLE IRRIGATIONS" ON THE CALORIC NYSTAGMUS OF THE CAT

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Cats underwent a series of "double irrigations" (simultaneous bilateral calorization with water of equal temperatures) The bilateral series did not affect nystagmic responses to unilateral caloric stimulation The data supply additional evidence for a central process in vestibular habituation and provide some hypotheses concerning the nature of the habituation mechanism

Recent studies have clearly demonstrated the phenomenon of nystagmus habituation (a response decline) resulting from repeated rotatory or caloric stimulation of the cat (e g, Capps & Collins, 1965, Collins, 1964 *a*, *b*, Crampton, 1962 *a* *b*, Henriksson, Kohut & Fernandez, 1961) Its acquisition has been regarded as a learning process, but there is little information available concerning the locus and nature of the attendant structural changes

Results reported by Hernandez-Peon & Brust-Carmona (1961) and by Fernandez & Schmidt (1962 *a*, *b*) indicate that removal of the neo-cortex of the cat does not prevent habituation The latter note, "In support of the opinion of Hernandez-Peon and Brust-Carmona, our data suggest strongly that the phenomenon takes place in some medullary and/or pontine structures It is reasonable to suspect that the locus is in the structures operating the vestibulo ocular reflex arc, that is, the vestibular nuclei and reticular formation" (Fernandez & Schmidt, 1962 *b*, pp 11–12)

Hamberger & Hyden (1949 *a*, *b*) have apparently provided the only reports of observed structural changes in habituation—a reduction of RNA and proteins in vestibular neurons That these alterations cause habituation is regarded by Fernandez & Schmidt (1962 *a*) as "debatable because no habituation occurs when repetitive stimulation is done under anesthesia" (p 19) The latter statement refers to a study by Fearing & Mowrer (1934) wherein it was noted that no habituation of head nystagmus occurred when pigeons were repetitively stimulated while under anesthetic Similarly,

Study conducted with the technical assistance of Mary Jayne Capps and Joseph F Duchon Assistance provided by H Gerald Hobelmann in the pilot experiments is gratefully acknowledged

teils seinen Anstrengungen zu verdanken, dass das Programm für Sprach- und Gehörrehabilitation ins Werk gesetzt und zu seinem gegenwärtigen Umfang erweitert werden konnte.

REFERENCES

BUNCH, C. C., 1929. Age variations in auditory acuity. *Arch. Otolaryng.* (Chic.), *9*: 625.
— 1931. Further observations on age variations in auditory acuity. *Arch. Otolaryng.* (Chic.), *13*: 170.
BUNCH, C. C. and RAIFORD, T. S., 1931. Race and sex variations in auditory acuity. *Arch. Otolaryng.* (Chic.), *13*: 423.
CAWTHORNE, T., 1951. Hearing and deafness. *Acta Otolaryng.* (Stockh.), *40*: 257.
CIOCCO, A., 1932. Observations on the hearing of 1980 individuals. *Laryngoscope 42*: 837.
DAVIS, H. (ed.), 1947. *Hearing and Deafness: a Guide for Laymen.* Rinehart and Co., Inc., New York.
DAVIS, H. (ed.) and SILVERMAN, S. R. (coed.), 1960. *Hearing and Deafness* (revised edition). Holt, Rinehart and Winston, Inc., New York.
EIFANDT, H. VON and SAXÉN, A., 1937. Pathologie und Klinik der Altersschwerhörigkeit. *Acta Otolaryng.* (Stockh.), Suppl. *23*.
GAETH, J. D.: A study of phonemic regression in relation to hearing loss. Doctoral Dissertation, Northwestern University, XVI, 1948.
GLORIG, A. and DAVIS, H., 1961. Age, noise and hearing loss. *Ann. Otol. Rhinol. and Laryngol. 70*: 556.
DEL GIUDICE, M. and AMOROTTI, A., 1960. Colesterolemia and presbyacusis. *Arch. Ital. Otol. 68*: 175.
HOOPLE, G. D., 1960. Care of hearing in the elderly. *Geriatrics 15*: 106.
JERGER, J. F., 1960. Audiological manifestations of lesions in the auditory nervous system. *Laryngoscope 70*: 417.
JØRGENSEN, M. B., 1961. Changes of aging in the inner ear. *Arch. Otolaryng.* (Chic.), *74*: 164.
KELLEY, N. H., 1939. A study in presbyacusis auditory loss with increasing age and its effect on perception of music and speech. *Arch. Otolaryng.* (Chic.), *29*: 506.
KLOTZ, R. E., and KILBANE, M., 1962. Hearing in an aging population: preliminary report. *New Engl. J. Med. 266*: 277.
LEISTI, T. J., 1949. Audiometric studies of presbyacusis. *Acta Otolaryng.* (Stockh.), *33*: 555.
Medical Audiology Workshop. Sponsored by the Div. of Otolaryngology of the University of Colorado School of Medicine. Estes Park, Colorado, July 30-August 3, 1962.
PESTALOZZA, G. and SHORE, I., 1955. Clinical evaluation of presbyacusis on the basis of different tests of auditory function. *Laryngoscope 65*: 1136.
RUSSO MACCLURE, I. S., 1948. Vascular disturbances of the internal ear (cochlear branch). *Rev. Bras. Otorinolaring. 8*: 3.
SAXÉN, H., 1952. Inner ear in presbyacusis. *Acta Otolaryng.* (Stockh.), *41*: 213.
SCHUKNECHT, H. F., 1955. Presbyacusis. *Laryngoscope 65*: 402.
SERCER, A. and KRMPOTIC, J., 1958. Über die Ursache der progressiven Altersschwerhörigkeit (presbyacusis). *Acta Otolaryng.* (Stockh.), Suppl. *143*: 6.

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TABLE 1 *Outline of the test procedure*

Animals	Pretest trials (unilateral calorics)	Test period	Posttest trials (unilateral calorics)
Experimental group			
20 E through 24 E	1 Right	15 double irrigations	Right
	2 Left		Left
	3 Right		Right
	4 Left		Left
25 E through 29 E	1 Left	15 double irrigations	Left
	2 Right		Right
	3 Left		Left
	4 Right		Right
Control group			
30 C through 34 C	1 Right	No stimulation	Right
	2 Left		Left
	3 Right		Right
	4 Left		Left
35 C through 39 C	1 Left	No stimulation	Left
	2 Right		Right
	3 Left		Left
	4 Right		Right

All trials were conducted in total darkness and all stimuli consisted of 30 sec of irrigation with water at 26°C Trials were conducted at intervals of twenty min Room lights were turned on when it was clear that no further response was forthcoming The minimum amount of time spent in illumination prior to initiating a trial was 10 minutes

Scoring—Duration, number of nystagmic movements (frequency), and slow-phase displacement of the eyes were scored from the point of stimulus termination to the last beat of primary nystagmus Frequency data were obtained simply by tabulating the number of nystagmic beats elicited by the stimulus Slow-phase measures represent the accumulated vertical distances, from peak to base-line, of all slow phase activity These latter values were converted to millivolts by means of an appropriate calibration signal

RESULTS

Nystagmus tracings obtained from an experimental and a control animal appear in Figs 1 and 2 respectively No marked pre-to-posttest changes are evident in spite of the fact that the experimental group underwent an intervening series of 15 double irrigations These 2 sets of tracings may be compared with Fig 3 which indicates the nystagmus response decline for an animal exposed to 17 consecutive unilateral irrigations at the same stimulus level

Hood & Pfaltz (1954) have reported little or no habituation of ocular nystagmus from an anesthetized rabbit. However, deep anesthesia prevents the evocation of a number of reflexes and many neural circuits appear to be damped out. The present study was designed to test, in awake animals, the effects of repeated stimulation of the vestibular end organs, conducted in such a way as to *prevent the elicitation of the nystagmic response*.

METHOD

Stimulator.—Cats were given series of caloric irrigations from a water bath maintained at a constant temperature by means of a Bronwill constant temperature circulator. The water passed from the bath through polyetheline tubing to a Y-shaped connector from whence it branched through two additional tubes, each terminating in a glass ear-insert. Water temperature in the bath was maintained such that it was 26°C upon introduction to the cat's external auditory meatus. Thus a single source provided the stimulus for both ears and the output, in terms of volume, rate of flow, and temperature of water, was the same for the two tubes.

Restraint.—Restraint was effected according to the technique of Henriksson, Fernandez & Kohut (1961). Animals were anesthetized several days prior to testing and holes were drilled transversely through their canine teeth. For testing, cats were wrapped in a towel and placed in a restraint box. A strand of piano wire was strung through the holes in their teeth and tightened by means of a device attached to the front of the box. The animals were thus firmly restrained with their heads elevated to an optimal position for caloric stimulation.

Recording.—Horizontal components of nystagmus were recorded on an Offner Type T Electroencephalograph (RC time constant, 3 sec). A pair of needle electrodes was inserted into the skin near the outer canthi, a ground electrode was clipped to one end of the wire inserted through the cat's teeth.

Procedure.—A control and an experimental group each consisted of 10 animals. Both groups received 4 test trials before (pre) and after (post) an interval during which the experimental group received a series of 15 double irrigations and the control animals were kept restrained but were not stimulated.

The pre- and posttest trials comprised 4 unilateral caloric irrigations, *presented alternately to the right and left ears. For each group, half the* animals received left-ear stimulation first, the remaining 5 animals were stimulated first in the right ear. The double irrigations consisted of simultaneous irrigation of both ears with the same stimulus temperature (see Table 1). Since a cool stimulus applied to a given ear drives the fast phase of nystagmus to the opposite side, simultaneous bilateral irrigation with cool water cancels out the horizontal component of nystagmus, and often induces a vertical response (cf. Fischer, 1956).

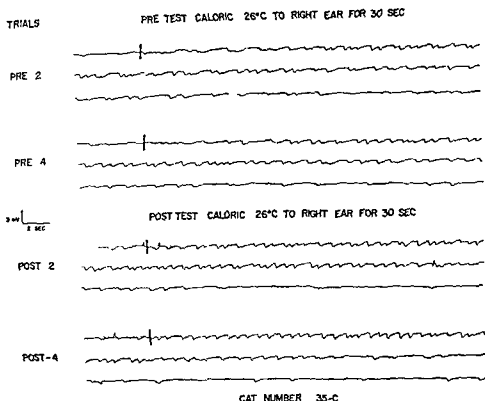


Fig 2 Nystagmus tracings from a cat in the control group Pre and posttests were separated by a 3 hour period of no stimulation

eye movements More frequently than not the response had a directional component, but it was completely consistent from trial to trial *in only one animal* It is of interest that animals which showed a greater output to stimulation of one side did not necessarily produce more double irrigation responses in that direction

Some of the nystagmus recorded during the double irrigations undoubtedly contained a vertical component Subsequent tests using other animals were conducted with electrodes of reduced size positioned to pick up horizontal and vertical movements independently In some cases a vertical component was evident after irrigation but in others only a weak horizontal response or random eye movements appeared Further testing indicated that the standard size electrodes employed in this study positioned by the *outer canthi* picked up some of the vertical component and thereby magnified the horizontal tracing

DISCUSSION

The present data indicate that in an awake cat repeated stimulation of the peripheral vestibular system is not of itself conducive to nystagmus

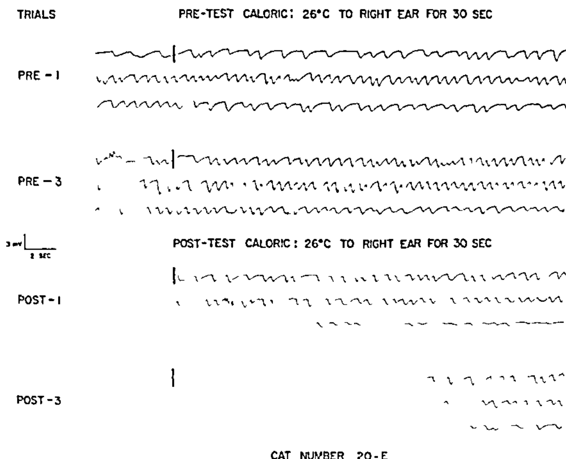


Fig. 1 Nystagmus tracings from a cat in the experimental group Fifteen double irrigations were administered between the pre and posttests

Average nystagmus duration, frequency, and slow-phase output are plotted in Fig 4 for the pre- and posttest data of both the experimental and control groups Some trial-to-trial variability in output between the groups is evident but such differences are not unusual for samples of this size The striking difference in output favoring right over left ears in the experimental group is accounted for primarily by a marked directional preponderance (favoring right-ear stimulation by factors ranging from 2–8, depending upon the cat and the measure) from the 2 animals of the group which produced the most nystagmus However, there was also a persistent, but a lesser, tendency for right-ear irrigations to result in more output than those of the left ear

A comparison of the control and experimental cats with a group of 10 cats from another study appears in Fig 5 It is clear that the decline from pre- to posttest for both the control and experimental animals is no greater than that which would have occurred had the pre- and posttest trials been administered consecutively, i e, without the double irrigations (experimental group) or without the intervening period of no stimulation (control group)

The double irrigations never resulted in a complete absence of recorded

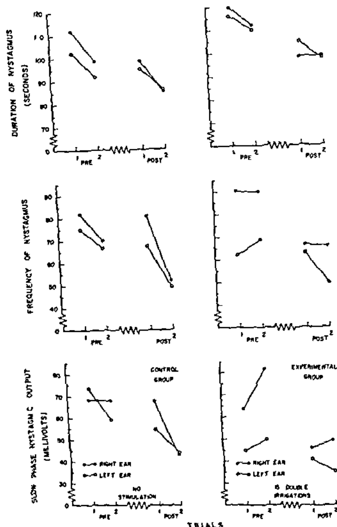


Fig. 4. Average nystagmus duration, frequency and slow phase output for the experimental and the control groups. The strikingly higher right ear output for the experimental animals is due primarily to a marked directional preponderance exhibited by two cats.

Collins, 1964 *a*, *b*; Crampton & Brown, 1964; Guedry, Collins & Graybiel, 1964).

The hyper-polarization and depolarization concepts proffered by Fluur & Mendel (1962 *a*, *b*) is a part of the habituation process might also be applicable here in a somewhat modified form. However, their data and predictions, based on human studies, may not hold for the cat. For example, they indicate that if caloric nystagmus were elicited alternately in opposite directions, no habituation would occur in man (Fluur & Mendel, 1962 *b*). This is not true for the cat, as the present pre- and posttest control data

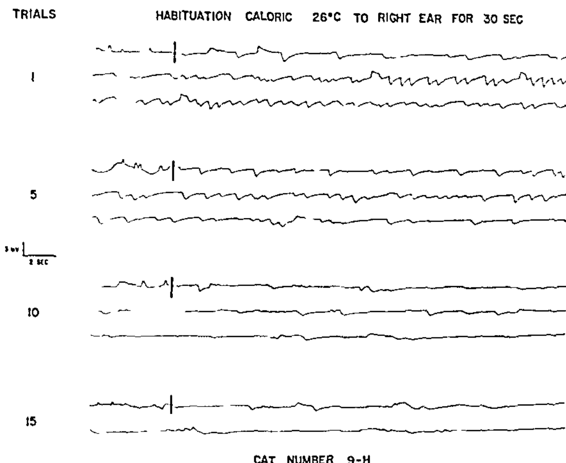


Fig. 3. Nystagmus tracings from a cat exposed to 17 consecutive unilateral caloric irrigations. The decline with repeated testing is clear.

habituation. As such they provide an additional bit of evidence for the central locus of the habituation mechanism, confirmation of the results of Fearing & Mowrer (1934) and of Hood & Pfaltz (1954) and, perhaps, some testable hypotheses as to the specification of the relevant center.

Since caloric irrigation, in deflecting the cupula, must result in a transmission of signals through the vestibular nucleus, it would appear either that the locus of the habituation process is at some level above the vestibular nuclei, or that some efferent feedback from higher centers to the nucleus (or to the crista) is required. If changes similar to those reported by Hamberger & Hydén (1949 a, b) occur in the vestibular nucleus purely as a function of repeated cupula deflection, then they cannot mediate the process of habituation as measured by nystagmus output. However, the neuronal changes may appear only as a result of efferent stimulation emanating from higher levels, perhaps in the reticular formation, and it is possible that such feedback activity may be inhibited either by compensatory balancing of input in the reticular system (from double irrigations) or by anesthesia. Further, habituation may be limited to the specific neural pattern generated by activity from combinations of the semicircular canals, or to the plane in which the evoked nystagmus occurs (Capps & Collins, 1965,

indicate, and as has been reported by Henriksson, Kohut & Fernandez (1961) for unilateral caloric irrigation, and by Crampton & Schwam (1961), using rotation.

RÉSUMÉ

Des chats reçurent une série d'irrigations des deux oreilles (calorisation bilatérale simultanée employant de l'eau de la même température dans les deux oreilles). La série bilatérale n'influença pas les réponses nystagmiques à la stimulation calorique unilatérale. Les données fournissent du témoignage additionnel d'un procédé central de l'adaptation vestibulaire et aussi des hypothèses à l'égard de la nature du mécanisme d'adaptation.

ZUSAMMENFASSUNG

Katzen wurden einer Serie beidseitiger Ohrspulungen (gleichseitige bilaterale Kalorisierung mit Wasser von gleicher Temperatur) unterzogen. Die beidseitige Spulung hatte keinen Einfluss auf die durch einseitige kalorische Reizung ausgelösten nystagmischen Reaktionen. Die Resultate liefern einen zusätzlichen Beweis für einen zentralen Vorgang in vestibulärer Gewöhnung und führen zu verschiedenen Hypothesen über die Art des Gewöhnungsmechanismus.

REFERENCES

Capps, M. J., and Collins, W. E., 1965. Effects of bilateral caloric habituation on vestibular nystagmus in the cat. *Acta Otolaryng. (Stockh.)* (in press).

Collins, W. E., 1964 *a*. Nystagmus responses of the cat to rotation and to directionally equivalent and non-equivalent stimuli after unilateral caloric habituation. *Acta Otolaryng. (Stockh.)* (in press).

— 1964 *b*. Primary, secondary and caloric nystagmus of the cat following habituation to rotation. *J. Comp. Physiol. Psychol. 57*, 417-421.

Crampton, G. H., 1962 *a*. Directional imbalance of vestibular nystagmus in cat following repeated unidirectional angular acceleration. *Acta Otolaryng. (Stockh.)* 55, 41-48.

— 1962 *b*. Effects of visual experience on vestibular nystagmus habituation in the cat. *Acta Otolaryng. (Stockh.)* 55, 516-526.

Crampton, G. H., and Brown, J. H., 1964. Repeated stimulation of vertical semicircular canals in cat does not habituate horizontal nystagmus. *Acta Otolaryng. (Stockh.)* (in press).

Crampton, G. H., and Schwam, W. J., 1961. Effects of arousal reaction on nystagmus habituation in the cat. *Amer. J. Physiol. 200*, 29-33.

Fearing, F., and Mowrer, O. H., 1934. The effect of general anesthesia upon the experimental reduction of vestibular nystagmus. *J. Gen. Psychol. 11*, 133-144.

Fernandez, C., and Schmidt, R., 1962 *a*. Studies on habituation of vestibular reflexes. II. Effect of caloric stimulation in decorticated cats. *Ann. Otol. 71*, 299-321.

— 1962 *b*. Studies in habituation of vestibular reflexes. III. A revision. *Laryngoscope 72*, 939-953.

Fischer, J. J. *The Labyrinth.* New York: Grune & Stratton, 1956.

Fluur, E., and Mendel, L., 1962 *a*. Habituation, efference and vestibular interplay. I. Monaural caloric habituation. *Acta Otolaryng. (Stockh.)* 55, 65-80.

— 1962 *b*. Habituation, efference and vestibular interplay. II. Combined caloric habituation. *Acta Otolaryng. (Stockh.)* 55, 136-144.

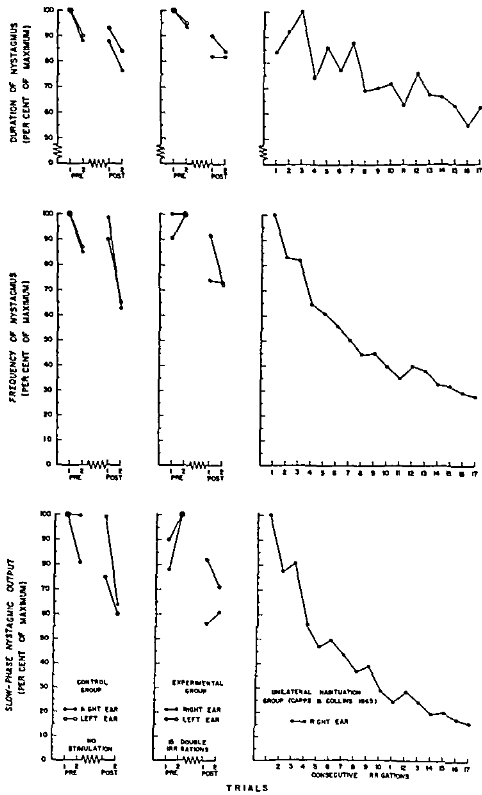


Fig. 5. A comparison of pre- and posttest data for the experimental and control animals with data obtained from a group of cats exposed to 17 consecutive unilateral caloric irrigations (Capps & Collins 1965). It is clear that the double irrigations had no effect on nystagmus habituation.

indicate, and as has been reported by Henriksson Kohut & Fernandez (1961) for unilateral caloric irrigation and by Crampton & Schwam (1961), using rotation

RESUME

Des chats recurent une serie d irrigations des deux oreilles (calorisation bilaterale simultanee employant de l eau de la meme temperature dans les deux oreilles) La serie bilaterale n influença pas les reponses nystagmiques a la stimulation calorique unilaterale Les donnees fournissent du temoignage additionnel d un procede central de l adaptation vestibulaire et aussi des hypotheses a l egard de la nature du mecanisme d adaptation

ZUSAMMENFASSUNG

Katzen wurden einer Serie beidseitiger Ohrspulungen (gleichseitige bilaterale *Kalorisierung mit Wasser von gleicher Temperatur*) unterzogen Die beidseitige Spulung hatte keinen Einfluss auf die durch einseitige kalorische Reizung ausgelösten nystagmischen Reaktionen Die Resultate liefern einen zusätzlichen Beweis fur einen zentralen Vorgang in vestibulärer Gewohnung und fuhren zu verschiedenen Hypothesen uber die Art des Gewohnungsmechanismus

REFERENCES

CAPPS M J, and COLLINS, W E, 1965 Effects of bilateral caloric habituation on vestibular nystagmus in the cat *Acta Otolaryng (Stockh)* (in press)

COLLINS, W E, *1964a* Nystagmus responses of the cat to rotation and to directionally equivalent and non equivalent stimuli after unilateral caloric habituation *Acta Otolaryng (Stockh)* (in press)

1964b Primary secondary and caloric nystagmus of the cat following habituation to rotation *J Comp Physiol Psychol* 57 417 421

CRAMPTON G H, 1962*a* Directional imbalance of vestibular *nystagmus in* cat following repeated unidirectional angular acceleration *Acta Otolaryng (Stockh)* 55 41 48

— 1962*b* Effects of visual experience on vestibular nystagmus habituation in the cat *Acta Otolaryng (Stockh)* 55 516 526

CRAMPTON G H, and BROWN J H, 1964 Repeated stimulation of vertical semicircular canals in cat does not habituate *horizontal nystagmus* *Acta Otolaryng (Stockh)* (In press)

CRAMPTON G H, and SCHWAM W J, 1961 Effects *of arousal* reaction on nystagmus habituation in the cat *Amer J Physiol* 200 29 33

FEARN D and M [illegible] thesia upon the experi [illegible] 133–144

FER [illegible] vestibular reflexes II [illegible] stimulation in *decorticated* cats *Ann Otol*, 71 299–321

— 1962*b* Studies in habituation of vestibular *reflexes* III A revision *Laryngoscope* [illegible] 939 953

FISCHER J J *The Labyrinth* New York Grune & Stratton 1956

FLUUR E, and MENDEL, L, *1962a* Habituation efference and vestibular interplay I Monaural caloric habituation *Acta Otolaryng (Stockh)* 55 65–80

1962*b* Habituation efference and vestibular interplay II Combined caloric habituation *Acta Otolaryng (Stockh)* 55 136–144

Guedry, F. E., Collins, W. E. and Graybiel, A., 1964. Vestibular habituation during repetitive complex stimulation. A study of transfer effects. *J. Appl. Physiol.* (in press)

Hamberger, C. A. and Hydén, H. 1949 *a*. Production of nucleoproteins in the vestibular ganglion. *Acta Oto-laryng. (Stockh.)*, Suppl. 75: 53–81.

— 1949 *b*. Transneuronal chemical changes in Deiters' nucleus. *Acta Oto-laryng. (Stockh.)*, Suppl. 75: 83–113.

Henriksson, N. G., Fernandez, C., and Kohut, R., 1961. The caloric test in the cat. *Acta Oto-laryng. (Stockh.)*, 53: 21–32.

Henriksson, N. G., Kohut, R. and Fernandez, C., 1961. Studies on habituation of vestibular reflexes. I. Effect of repetitive caloric test. *Acta Oto-laryng. (Stockh.)*, 53: 333–349.

Hernandez-Peón, R., and Brust-Carmona, H., 1961. Functional role of subcortical structures in habituation and conditioning. In Delafresnaye, J. F. (Ed.) *Brain Mechanisms and Learning*. Oxford: Blackwell Scientific Publications, pp. 393–412.

Hood, J. D. and Pfaltz, C. R., 1954. Observations upon the effects of repeated stimulation upon rotational and caloric nystagmus. *J. Physiol.* 125: 130–144.

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OLFACTORY NEUROBLASTOMA

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The literature concerning olfactory neuroblastoma, a rare and often malignant tumour, is reviewed. The first case of the tumour was described in 1924 by Berger *et al.* and reports on some ninety cases are to be found in world literature. The present author emphasizes that more published reports on such cases with an adequate period of observation are required to throw light on many problems concerning this tumour. A case of metastasizing olfactory neuroblastoma in a 60-year-old patient is described. The tumour was fairly resistant to radiotherapy. Cytostatic treatment with triethylene thiophosphoramide (Thiotepa) gave a complete remission of five weeks' duration after the first course of therapy and a partial remission of two weeks' duration after the second course of therapy. The patient died six and a half months after the appearance of the first symptoms.

Olfactory neuroblastoma is a rare tumour, only some 90 cases have been reported on in world literature. The first report on such a case was published in 1924 by Berger *et al.* who called the tumour "esthesioneuro-épithéliome olfactif". The tumour consisted of an undifferentiated neuroectodermal structure reminiscent of that seen in tumours of the adrenal medulla and the ganglia of the sympathetic nervous system. True neuroepithelial rosettes—small circles lined with columnar cells—were visible in the histological picture of the tumour; they were taken to represent neoplastic analogues of supporting cells of the olfactory mucous membrane. The fibrils and small undifferentiated nuclei were analogous to true neural fibrils. Two years later (1926) a report on a similar case of tumour but with a somewhat different histological picture was published by Berger & Coutard. This tumour they called "esthesioneurocytome olfactif", and it was regarded as representing a somewhat more differentiated variety of the same tumour. They readily admitted a pattern highly reminiscent of sympathomas but pointed out that tumours originating from the sympathetic nervous system are never seen outside the adrenal glands and large sympathetic trunks. The histological picture showed no true neuroepithelial rosettes, but there were so-called pseudorosettes composed of small circles of poorly differentiated cells.

The reports published by Berger and his co-workers were soon followed by a number of French papers (Portmann *et al* 1929 Escat 1931 Massier & Duguet 1937 Grigouroff & Dulac 1943 Portmann & Baillard 1947 Wild *et al* 1949 Martin *et al* 1949 Rossert & Chesseboeuf 1950 Huet 1950 Piquet 1950 Terracol *et al* 1951 Aboulker 1951 Bose & Browaeys 1952 Huet *et al* 1953 Girard & LeBlond 1957 David *et al* 1960 Calvet *et al* 1962 Mollier 1962 Aubry *et al* 1963 Andre & Lacourreye 1964) Portuguese papers (Tavares 1941 Ribeiro 1946 Celestino da Costa 1946 Alves 1952) and Italian papers (Jemmi 1947 Bozzi & Cecati Cassin 1961) The tumour was also described in many German papers (Ferplan & Rudofsky 1926 Lobeel 1929 Adler 1930 Mittelbach & Woletz 1935 Figler 1937 Kroath 1939) The earliest American reports were published in 1951 by Shall & Linchael and by Seaman and were followed by these of Fruhling & Wild 1951 Fisher 1955 McCormack & Harris 1955 Mendeloff 1957 Riemenschneider & Prior 1958 Sirtori *et al* 1958 Aldave & Galliger 1959 Church & Uhler 1959 Holland *et al* 1959 Mettler 1959 King 1959 Kramer & McCoy 1959 Obert *et al* 1960 Mashberg *et al* 1960 Palmer *et al* 1960 Dibble & Brown 1961 Hutter *et al* 1963 There is in addition a Czechoslovakian (Hlasicova & Vacek 1952) a Brazilian (Lang & Fagundes 1959) and a Swiss report (Largiader 1961)

Even before Berger *et al* (1924) the Germans Schmidt (1900) Chiari (1901) and Sussenguth (1909) the American Clark (1905) and the French Anglade & Philip (1920) had reported on cases of a tumour termed as glioma of the nose According to their descriptions the tumour reminded very much of olfactory neuroblastomas Both Chiari (1901) and Sussenguth (1909) assumed that the tumour had originated from the olfactory nerve

To indicate the rarity of this tumour it may be mentioned that Aldave & Galliger (1959) found only one such tumour among the 40 000 specimens they examined in a period of 13 years of cancerological consultation Ringertz (1938) points out that in his histopathologic investigation of 391 cases of chiefly malignant tumours in the nasal and paranasal cavities and maxilla he did not find one case of neuroblastoma Nor did Vaheri & Setala (1962) mention any case of this tumour among their 121 cases of malignant tumours of the paranasal sinuses

On the other hand there are reports which suggest that olfactory neuroblastoma may not be so rare as it seems McCormack & Harris (1955) found five cases of mistaken diagnosis in their review of about 80 cases of true neoplasms of the nasal cavity including tumours of the antrum and lateral nasal walls From their findings it seems somewhat surprisingly that olfactory neuroblastomas comprise about three per cent of intranasal tumours excluding polyps Obert *et al* (1960) made a systematic study of all cases of intranasal neoplasms seen at Mayo Clinic between 1931 and 1957 Slides of all lesions except those recorded as polyps squamous cell carcinoma (Grades I and II) and adenocarcinoma (Grades I and II)

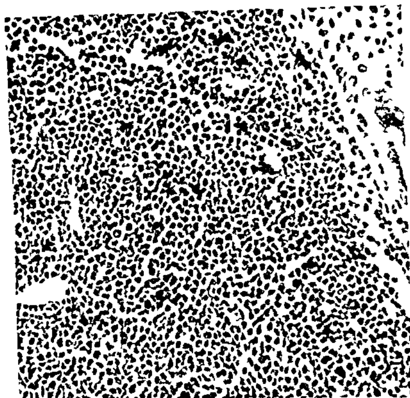


Fig. 1 Olfactory neuroblastoma Packed cell infiltrate of tumour cells confined to the root sheath of a hair Hemalaun eosin staining × 350

were reviewed these latter slides were excluded since it was felt that any tumour so classified would not have been confused with neurogenic neoplasms The study covered 504 cases eight of which the authors felt satisfied criteria for the diagnosis of olfactory neuroblastoma

Site of Origin

In the vast majority of cases the tumour had arisen high in the nose in the olfactory region Berger *et al* (1924) considered that the tumour originated from the sensory cells of the olfactory mucosa Other sites of origin have also been suggested Escat (1931) assumed that it was the sphenopalatine ganglion Martin *et al* (1949) suggest it may have been the ganglion of Locy a small organ situated in the anterior part of the olfactory region which consists of ganglion cells and sympathetic fibres

Diagnosis and Differential Diagnosis

The tumour often causes a progressive and permanent obstruction of the nasal cavity For a long time there is no pain but epistaxis often occurs

The tumour grows gradually by infiltration, frequently in a certain fixed main direction: laterally towards the orbit, upward towards the frontal sinus and endocranium, backward towards the choana, downward towards the maxillary sinus, or medially towards the other nasal cavity. By the time the patient seeks medical advice an enlargement of the root of the nose is a frequent finding. Age and sex play no role in the development of the tumour.

The diagnosis is naturally based on the biopsy specimen. The difficulty is, however, that because of its rarity the tumour can easily be confused histologically with other small-cell neoplasms. This is true especially of undifferentiated carcinomas and lymphosarcomas. Erroneous diagnoses have been detected by McCormack & Harris (1955), and by Obert *et al.* (1960). As early as 1926 Berger & Coutard assumed that a number of the lymphangiosarcomas of the nasopharynx previously reported on by other authors were probably examples of olfactory neuroblastomas.

All olfactory neuroblastomas are, as Berger & Coutard (1926) pointed out, to be classified as malignant tumours, though on the whole neurocytoma has been considered more malignant than neuroepithelioma. Most of the reported cases of olfactory neuroblastoma have been of the neurocytoma pattern. More published cases of both types are required before an opinion can be advanced on the degree of malignancy and whether any major difference exists between the two types on this point. In the first cases of olfactory neuroblastoma published by Berger *et al.* (1924) there was a cervical metastasis. McCormack & Harris (1955) reported metastases in the cervical lymph nodes, scalp, lungs and bones, Seaman (1951) in the cervical lymph nodes, mediastinum and pleura, Mendeloff (1957) in the lungs, pleura and mediastinum, Riemenschneider & Prior (1958) in the spinal cord and brain, Holland *et al.* (1959) in the lungs, pleura and liver, Aubry *et al.* (1963) and Hutter *et al.* (1963) in the cervical lymph nodes.

Treatment and Prognosis

Radiotherapy, either alone or in combination with surgical extirpation has been used for the treatment of olfactory neuroblastomas, though the tumour is not particularly sensitive to radiation. This is especially true of the most frequent variety of the tumour, that designated by Berger & Coutard (1926) as neurocytoma. Surgical extirpation is often technically difficult since the tumour is located high in the nose. Treatment is further complicated by the occurrence of metastases. The result of treatment is difficult to predict, partly because relatively few cases have so far been reported on, and partly because the follow-up period in many of the published reports is far too short. The prognosis, however, must be considered doubtful.

The patient reported on below received cytostatic treatment after radio



Fig. 2. Smaller scale enlargement of the tumour region showing infiltration in connective and fat tissue. Hemalaun eosin staining. × 150.

therapy had failed. No reports on experience of cytostatic treatment of olfactory neuroblastoma have previously been published, though Mendeloff (1957) mentioned briefly that one of his patients received nitrogen mustard and radiation therapy, after which the tumour was found to be reduced in size.

CASE REPORT

The patient was a carpenter aged 60 years. Early in October 1962 he noticed a slight swelling and reddening left of the root of the nose. After the condition had persisted for three weeks the local medical officer referred the patient to the Department of Ophthalmology of our Hospital, suspecting phlegmonous dacryocystitis. The ophthalmologist soon discovered that dacryocystitis was not involved; he nevertheless made an incision in the region of the lacrymal sac but without finding pus. The tumorous swelling, which was completely painless, grew rapidly. Radiographs showed an opacity of the left ethmoidal, maxillary and frontal sinuses; the eye bulb showed an increasing lateral and forward dislocation. A biopsy specimen was taken, and the pathologist reported that its structure suggested a high degree of malignancy and rapid growth. Exact

classification of the tumour was difficult because of its anaplastic nature. The nuclei were very close to one another. The appearance of the cells, and the intercellular fibrils in some parts of the tumour, led to a diagnosis of sympathicoblastoma. The tumour grew very fast from the left side of the root of the nose across the forehead, both eyelids, into the orbit, laterally of the eye and on the left cheek. A growing bulge covered by intact mucosa could be seen high in the left nasal cavity At this stage the neoplasm was considered inoperable, and radiotherapy was started late in November. The tumour was given a skin dose of 6300 r. Halfway through the course of radiotherapy a cervical metastasis was found At the end of January, a fortnight after the termination of radiotherapy, metastases were suddenly seen on both sides of the neck and on the face The primary tumour, which was not particularly sensitive to irradiation, had by this time decreased slightly in size Bilateral recurrent laryngeal nerve paralysis occurred Metastases in the right lung were seen on x-ray picture

Cytostatic treatment with triethylene thiophosphoramide (Thiotepa) was inaugurated at the beginning of February. The patient was given a dose of 15 mg daily for nine days, with remarkable results: by the end of treatment the primary tumour and all metastases had disappeared, nor could the pulmonary metastases be seen on radiographs. The vocal cords had normal mobility, and the patient's voice was clear The left eye was blind as a result of the earlier radiotherapy, but the patient was otherwise symptom-free for a period of five weeks, after which there was again a fast-growing tumour left of the root of the nose Metastases appeared on the neck and face, the laryngeal paralysis returned Cytostatic treatment with triethylene thiophosphoramide was re-started, the dose again being 15 mg per day for nine days The result of treatment was again dramatic, and the patient became practically symptom-free One metastasis remained on the neck though it had diminished in size during the course of treatment The vocal cords again moved symmetrically This time, however, the relative freedom from symptoms lasted only a fortnight The primary tumour grew again rapidly, and metastases appeared on both sides of the neck and on the face The bilateral recurrent laryngeal nerve paralysis returned Three weeks after the termination of treatment, on April 21, 1963, the patient died, six and a half months after the appearance of the first symptoms of the disease Necropsy was not performed

DISCUSSION

The histological diagnosis of the tumour described above was sympathicoblastoma No distinction, either in clinical behaviour or in histological classification, is apparent between tumours regarded as olfactory sympathicoblastomas and the so-called esthesioneurocytomas, as has already been pointed out by Berger & Coutard (1926), Grigouroff & Dulac (1943), Bosc & Browaeys (1952) and Obert *et al* (1960) There is little

point in further classifying olfactory neuroblastomas since no typical features consistently and definitely common to any sub group can be distinguished in the histological or the clinical picture It is rather a question of various degrees of differentiation of the same tumour So called pseudorosettes could also be seen occasionally in the histological picture of this tumour though it is often a question of interpretation as to which cellular structures are to be considered pseudorosettes and which are not It is also possible—at least with a little imagination—to observe similar cell accumulations in other tumours too Many of the problems concerning olfactory neuroblastomas remain unsolved but the same applies to many other malignant tumours Opinions differ on the exact site of origination the degree of malignancy and on the degree of sensitivity to irradiation The treatment of the localized tumour has usually been based on a combination of surgery and radiotherapy It was encouraging to find that after cytostatic therapy of the reported metastasizing tumour there was a complete remission of five weeks duration following the first course of therapy, and a partial remission of two weeks duration after the second On both occasions the bilateral recurrent laryngeal nerve paralysis vanished an indication that the metastases of the mediastinum had also disappeared One can reasonably assume that cytostatics with increased affinity to tumour cells and reduced affinity to healthy tissue cells will be developed in the future

ZUSAMMENFASSUNG

Die Literatur uber das Neuroblastom des Olfactorius wird referiert Der Tumor ist selten und sein Verlauf in vielen Fällen sehr maligne Den ersten Fall von diesem Tumor haben 1924 Berger Luc und Richard beschrieben In der Weltliteratur sind bisher an die 90 Fälle veröffentlicht worden Der Autor weist *darauf hin* dass eine grossere Anzahl von publizierten Fallen mit genugend langer Observationszeit erforderlich wäre um viele mit diesem Tumor verknupfte Probleme losen zu konnen

Ein Fall von metastasierendem Neuroblastom des Olfactorius bei einem 60jahrigen Mann wird beschrieben Der Tumor war gegen die rontgenologische Behandlung ziemlich resistent Zytostatische Therapie mit Triathylenthiophosphoramid (Thiotepa) ergab nach der ersten Behandlungsserie eine vollständige Remission von *funfw* öchentlicher Dauer und nach der zweiten Behandlungsreihe eine partielle Remission von zwei Wochen Der Patient starb 6 Monate nach dem Auftreten der ersten Symptome

REFERENCES

ABOLKER M P, 19 1 Sympath blast me de la fosse nasale *Ann Ot Laryng (Lar* 13 101

ADLER, H, 1930 *Ein* Beitrag zu neurogenen Geschwulsten der Nase *Z Hals Nas Ohrenheilk* 2 30

ALASSY A, and GALLAGER H S, 19 Olfactory esthesioneuroepithelioma Report of a case and review of the literature *Arch Path Chic* 6 43

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REFERENCES

Aboulker M I, 1951 Sympathoblastome de la fosse nasale *Ann Otolaryng (Par)* 68 101

Adler H., 1930 Ein Beitrag zu neurogenen Geschwulsten der Nase *Z Hals Nas Ohrenheilk* 26 305

Altmann A and Gallager H S 1959 Olfactory *esthesioneuroepithelioma* Report of a case and review of the literature *Arch Path (Chic)* 6 43

ALVES I DA S., 1952 Tres casos de neuroblastoma das fossas nasais *J Med (Porto) 19* 1125

ANDRÉ P., and LACCOURREYE, H 1964 Esthésioneuroépitheliome de la fosse nasale *Ann Otolaryng (Par), 81* 280

ANGLADE and PHILIP, 1920 Le gliome des fosses nasales *Presse Med 28* 464

AUBRY M LENHER J., JOST, G and CHOLARD G H., 1963 Les tumeurs de la placode olfactive *Ann Otolaryng (Par) 80*, 50

BERGER L., and COUTARD, H., 1926 L'esthésioneurocytome olfactif *Bull Ass Franc Cancer 15* 404

BERGER L., LUC and RICHARD 1924 L'esthésioneuroépithéliome olfactif *Bull Ass Franc Cancer 13* 410

BOSC P., and BROWAEYS 1952 Tumeur nerveuse des fosses nasales Un cas d'esthésioneurocytome *Ann Otolaryng (Par), 69* 246

BOZZI E., and CECATI CASSIN G., 1961 Simpatoblastoma etmoido mascellare *Arch Ital Otol 72* 843

CALVET, J., CLAUX J., LO R., and COLL, J., 1962 Les tumeurs de la placode olfactive *J Franc Otolaryng 11* 129

CELESTINO DA COSTA A 1946 Estudo histológico de un caso de neuro epitelioma olfactivo *Lisboa Med 23* 99

CHIARI H 1901 Gliomatöse Entartung des einen Tractus und Bulbus olfactorius bei Glioma cerebri *Deutsch Med Wschr 27* 716

CHURCH L E UHLER I V., and WASHINGTON D C., 1959 Olfactory Neuroblastoma *Oral Surg 12* 1040

CLARK J P., 1905 Glioma of the nose Report of two congenital cases *Amer J Med Sci 130* 769

CORMACK MC. L J., and HARRIS H E., 1955 Neurogenic tumors of the nasal fossa *J A M A 157* 318

DAVID M., MESSIMY R BERDET H., and PERTUISET B., 1960 Tumeur dite de la placode olfactive (esthesioneuro épithéliome) à developpement simultané cerebral et nasal *Presse Med 68* 1981

DIBLEE P A., and BROWN A K 1961 Esthesioneuroepithelioma *Laryngoscope 71* 192

EICKEN G., 1937 Drei seltene Geschwülste der oberen Luftwege (Fibrorhabdomyoma laryngis Neurofibroma laryngis Glioblastoma nasi) *Hals Nas Ohrenar E 28* 320

ESCAT E 1931 Le sympathome sphénoido ethmoidal n'aurait il pas son point de départ dans le ganglion spheno palatin? Origine suggérée par 2 observations *Ann Otolaryng (Par) 2* 828

FISHER E R 1955 Neuroblastomas of the nasal fossa *Arch Path (Chic) 60* 435

FRUHLING L and WILD C 1954 Olfactory esthesioneuroepitheliomas of Louis Berger *Arch Otolaryng (Chic) 60* 37

GIRAUD J CH and LEBROND R., 1957 Sympathome des fosses nasales *Ann Otolaryng (Par) 74* 111

GRIGOURIEFF G and DELAC G 1943 Neuroblastome des fosses nasales *Ann Otolaryng (Par) 7* 77

HOLLAND L C CUSTER R E BUTCHER J., and GABRIELS R W 1959 Olfactory neuroepithelioma (neuroblastoma) *Arch Otolaryng (Chic) 69* 724

HLASICOVÁ V and VACEK R 1952 Primarní neuroblastom v dutině nosní *Cas Lek Cesk 91* 1006

HUET P C 1950 in discussion of *Rossert and Chesselœuf Ann Otolaryng (Par) 6* 707

HUET P C LABAYLE J and PIERQUIN B 1953 Sur un nouveau cas d'esthesio neuroepitheliome olfactif *Ann Otolaryng (Par) 70* 780

HUTTER R V P LEWIS J S FOOTE F W Jr and TOLLEFSEN H R 1963 Esthesioneuroblastoma A clinical and pathological study *Am J Surg 106* 748

JEMMI, C., 1947 I tumori neurogeni del naso (gliomi e neuroblastomi) *Otorinolaring Ital* 15 149

KING J T., 1959 Olfactory neurocytoma (esthesioneuroepitheliome olfactif) case arising in the nasopharynx *Arch Otolaryng (Chic)* 69 729

KRAMER B M., and McCOY G., 1959 Treatment of lateral nasal wall tumors through lateral rhinotomy approach *Arch Otolaryng (Chic)* 70 132

KROATH F., 1959 Über eine seltene Geschwulstbildung im Bereich der Nase *Krebsarzt* 14 48

LANG, R., and FAGUNDES, L A., 1959 Neuroblastoma olfactivo *Rev Brasil Otorinolaring* 27 59

LARCIADÈR F., 1961 Ein seltener Nasentumor Das Aesthesioneuroepitheliom des Olfactorius *Pract Otorhinolaryng (Basel)* 23 353

MARTIN J F., DARGENT M., and GIGNOUX M., 1949 Les tumeurs nerveuses des fosses nasales *Ann Otolaryng (Par)* 66 18

MASHBERG A THOMA K H., WASILEWSKI E J., and PROVIDENCE R I., 1960 Olfactory neuroblastoma (esthesio neuroepithelioma) of the maxillary sinus *Oral Surg* 13 908

MASSIER A., and DUCUET J., 1937 Considerations sur un cas de neuroepitheliome des fosses nasales esthésioneuroépithéliome olfactif *Ann Otolaryng (Par)* 2 829

MENDELOFF J., 1957 The olfactory neuroepithelial tumors A review of the literature and report of six additional cases *Cancer* 10 944

METTLER D C., 1959 Olfactory neuroepithelioma *Portland Clin Bull* 13 41

MITTELBACH M., and WOLETZ F., 1935 Zwei Falle von Neurinom der Nase *Med Klin* 31 275

MOLLICA, V., 1962 Esthésio neuroblastome olfactif Considérations anatomo-cliniques et pathogenetiques *Rev Laryng (Bord)* 83 401

OBERT G J., DEVINE K D and McDONALD J R 1960 Olfactory neuroblastomas *Cancer* 13 205

PALMER, R F., DELANEY A J., and CANNON A., 1960 Olfactory esthesioneuroepithelioma Report of a case *Virginia Med Monthly* 8 146

PIQUET M 1950 Neurinome du rhino pharynx *Ann Otolaryng (Par)* 67 730

PORTMANN G and BEILLARD P F., 1947 Les tumeurs nerveuses des fosses nasales *Rev Laryng (Bord)* 68 1

PORTMANN BONNARD and MOREAU 1929 Sur un cas de tumeur nerveuse des fosses nasales (esthésioneuroblastome) *Acta Otolaryng (Stockh)* 13 52

RIBEIRO C S 1940 Sobre os tumores nervosos das fossas nasais *Portugal Med* 1 1

riginating from olfactory
759

the nasal and paranasal
suppl 27 1

ROSSERT and CHESSEBOEUF 1950 Tumeur nerveuse des fosses nasales *Ann Otolaryng (Par)* 6 707

SCHALL, L A and LINEBACK M., 1951 Primary intranasal neuroblastoma Report of 3 cases *Ann Otol* 60 221

SCHMIDT M B 1900 Über seltene Spaltbildungen im Bereiche des mittleren Stirnfortsatzes *Virchow Arch Path Anat* 162 340

SEAMAN W B 1951 Olfactory esthesioneuro-epitheliomas *Radiology* 57 541

SIRTORI C., CALEARO C and TEATINI C P., 1958 An uncommon case of neurogenic nasal tumor *Arch Otolaryng (Chic)* 67 93

SUSSENGUTH L, 1909 Über Nasengliome *Virchow Arch Path Anat*, 195 537

TAVARES, A., 1941 Tumores nervosos das fossas nasais *Portugal Med.*, 8 305

TERPLAN K and RUDOFSKY F., 1926 Über zwei neurogene Tumoren in der Nasen und Mundhohle *Z Hals Nas Ohrenheilk* 14 260

ALVES, L. DA S., 1952. Três casos de neuroblastoma das fossas nasais. *J. Med. (Porto)*, *19*, 1125.

ANDRE, P., and LACCOURREYE, H., 1964. Esthésioneuroépithéliome de la fosse nasale. *Ann. Otolaryng. (Par.)*, *81*, 280.

ANCLADE and PHILIP, 1920. Le gliome des fosses nasales. *Presse Méd.*, *28*, 464.

AUBRY, M., TEXIER, L., JOST, G., and CHOLARD, C.-H., 1963. Les tumeurs de la placode olfactive. *Ann. Otolaryng. (Par.)*, *80*, 56.

BERGER, L., and COUTARD, H., 1926. L'esthésioneurocytome olfactif. *Bull. Ass. Franc. Cancer*, *15*, 404.

BERGER, L., LUC and RICHARD, 1924. L'esthésioneuroépithéliome olfactif. *Bull. Ass. Franc. Cancer*, *13*, 410.

BOSC, P., and BROWAEYS, 1952. Tumeur nerveuse des fosses nasales. Un cas d'esthésioneurocytome. *Ann. Otolaryng. (Par.)*, *69*, 246.

BOZZI, E., and CIGATI CASSIS, G., 1961. Simpatoblastoma ethmoido-mascellare. *Arch. Ital. Otol.*, *72*, 843.

CALVET, J., CLAUX, J., LO, R., and COLL, J., 1962. Les tumeurs de la placode olfactive. *J. Franc. Otolaryng.*, *11*, 129.

CELESTINO DA COSTA, A., 1946. Estudo histológico de un caso de neuro-epitelioma olfactivo. *Lisboa Med.*, *23*, 91.

CHIARI, H., 1901. Gliomatöse Entartung des einen Tractus und Bulbus olfactorius bei Glioma cerebri. *Deutsch. Med. Wschr.*, *27*, 716.

CHURCH, L. E., UHLER, I. V., and WASHINGTON, D. C., 1959. Olfactory Neuroblastoma. *Oral Surg.*, *12*, 1040.

CLARK, J. P., 1905. Glioma of the nose. Report of two congenital cases. *Amer. J. Med. Sci.*, *130*, 709.

CORMACK, MC. L. J., and HARRIS, H. E., 1955. Neurogenic tumors of the nasal fossa. *J.A.M.A.*, *157*, 318.

DAVID, M., MESSIMY, R., BERDET, H., and PERTUISET, B., 1960. Tumeur dite de la placode olfactive (esthésioneuro-épithéliome) à développement simultané cérébral et nasal. *Presse Méd.*, *68*, 1981.

DIBBLE, P. A., and BROWN, A. K., 1961. Esthesioneuroepithelioma. *Laryngoscope*, *71*, 192.

EIGLER, G., 1937. Drei seltene Geschwülste der oberen Luftwege. (Fibrorhabdomyoma laryngis, Neurofibroma laryngis, Glioblastoma nasi.) *Hals-Nas. Ohrenarzt*, *28*, 320.

ESCAT, E., 1931. Le sympathome sphénoïdo-ethmoïdal n'aurait-il pas son point de départ dans le ganglion sphéno-palatin? Origine suggérée par 2 observations. *Ann. Otolaryng. (Par.)*, *2*, 828.

FISHER, E. R., 1955. Neuroblastomas of the nasal fossa. *Arch. Path. (Chic.)*, *60*, 435.

FRUHLING, L., and WILD, C., 1954. Olfactory esthesioneuroepitheliomas of Louis Berger. *Arch. Otolaryng. (Chic.)*, *60*, 37.

GIRAUD, J. CH., and LEBLOND, R., 1957. Sympathome des fosses nasales. *Ann. Otolaryng. (Par.)*, *74*, 111.

GRIGOURIOFF, G., and DELAC, G., 1913. Neuroblastome des fosses nasales. *Ann. Otolaryng. (Par.)*, *7-9*, 77.

HOLLAND, L. C., CESTER, R. P., BUTCHER, J., and GARLICHS, R. W., 1959. Olfactory neuroepithelioma (neuroblastoma). *Arch. Otolaryng. (Chic.)*, *69*, 724.

HLASICOVÁ, V., and VACEK, R., 1952. Primární neuroblastom v dutině nosní. *Čas. Lék. česk.*, *91*, 1006.

HUET, P. C., 1950, in discussion of *Rossert and Chesseboeuf*. *Ann. Otolaryng. (Par.)*, *67*, 707.

HUET, P. C., LABAYLE, J., and PIQUETS, B., 1953. Sur un nouveau cas d'esthésio-neuroépithéliome olfactif. *Ann. Otolaryng. (Par.)*, *70*, 786.

HUTTER, R. V. P., LEWIS, J. S., FOOTE, F. W., JR., and TOLLEFSEN, H. R., 1963. Esthesioneuroblastoma. A clinical and pathological study. *Am. J. Surg.*, *106*, 748.

THE ADRENERGIC INNERVATION OF THE NASAL MUCOSA OF CERTAIN MAMMALS

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The distribution and the morphological construction of the adrenergic innervation to various sections of the vascular bed in the nasal mucosa of certain mammals was studied by means of the highly sensitive and specific fluorescence method of Falck & Hillarp. Noradrenaline was found to be present within typical adrenergic nerve terminals running in anastomosing strands of an autonomic ground plexus which surround and is directly superimposed on the muscle layer. The terminals practically never penetrated into this layer.

The arteries, arterioles and veins of the nasal mucosa were surrounded by a rich adrenergic plexus. The very rich adrenergic plexus surrounding the wide veins of the erectile tissue in the inferior concha is considered to be of great importance in regulating the blood flow through the nasal mucosa. Special attention was paid to the possible occurrence of sphincters with a rich adrenergic innervation. No differentiated innervation structures were observed, however. No adrenergic fibres were present around the glands of the nasal mucosa.

INTRODUCTION

With the help of a highly specific and sensitive fluorescence method, developed by Falck & Hillarp, it has become possible to study the cellular localization of monoamines in the nervous system (Falck, 1962, Carlsson, Falck & Hillarp, 1962, Hamberger & Norberg, 1963, Dahlström & Fuxe, 1964, Norberg & Hamberger, 1964). Thanks to their high content of the adrenergic transmitter, noradrenaline, the adrenergic nerve terminals can be visualized everywhere in the body. The adrenergic innervation of blood-vessels in skeletal muscle has previously been studied in this way (Fuxe & Sedvall, 1964, 1965), but no studies have so far been made with this method on the nasal mucosa including the highly vascularized lamina propria of, *inter alia* the inferior concha. The vasomotors of this specialized vascular bed, which shows pronounced reactions, are of great interest from both the morphological and the physiological points of view.

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Ferracol, J., Guerrier, Y., and Barjon, P., 1951. Un cas de tumeur nerveuse rare des fosses nasales: sympathome sympathogonique. *Rev. Laryng. (Bord.)* 72: 603.

Tollck, A., 1929. Über das Vorkommen und die Entstehung neurogener Geschwülste im Bereiche der Nase. *Z. Hals. Nas. Ohrenheilk.* 23: 329.

Vaheri, E., and Setälä, H., 1962. Malignant tumours of paranasal sinuses. *Acta Otolaryng. (Stockh.)*, 54: 561.

Wild, C., Frühling, L., and Klotz, G., 1949. A propos d'un cas de tumeur nerveuse rare des fosses nasales: l'esthésio-neuro-épithéliome olfactif. *Rev. Laryng. (Bord.)* 70: 137.

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FIG 1 Inferior concha of normal rabbit Cross-section A high amount of green fluorescent material is observed around the wide veins of the erectile tissue (*A*) and around the arteries (*B*) The nasal epithelium is seen at *C* and the cartilage at *D* Fluorescence microphotograph 30×

and postcapillary vessels it cannot be excluded that some of the postcapillary vessels also receive such terminals The capillaries themselves, on the other hand do not seem to receive any adrenergic terminals since practically all of the fluorescent fibres were connected to larger blood vessels

In all the mammals studied, the fluorescence microscopical picture in the nasal mucosa of the inferior concha is dominated by a rich adrenergic plexus surrounding the thin muscle layer of the wide veins (lacunes) of the erectile tissue ('venose Schwellgewebe') (Figs 1, 2 4, and 5) The other parts of the nasal mucosa also have a fairly rich adrenergic innervation of the veins within the tunica propria The veins receiving the blood



FIG 2 Inferior concha of normal rabbit Tangential section *A* high amount of green fluorescent material is present surrounding the wide veins of the erectile tissue (*A*) and the arteries (*B*) The nasal epithelium is present at *C* Fluorescence microphotograph 40×

MATERIAL AND METHODS

Normal rats (20), guinea pigs (10), rabbits (10), and cats (5) were used. Reserpine (Serpasil®, Ciba) treatment was performed 24 hours before killing in 5 rats (10 mg/kg), 4 guinea pigs (20 mg/kg), 4 rabbits (5 mg/kg), and 3 cats (5 mg/kg). All injections were intraperitoneal except in the case of the rabbits, which were injected i.v. Other doses and times before killing were also studied in the rabbit. 12 rabbits were divided into groups of four and killed 2, 4, and 12 hours after the injection of a dose of 5 mg/kg. 9 rabbits were divided into groups of three and killed 24 hours after the injection of 0.05 mg/kg, 0.2 mg/kg, and 1 mg/kg of reserpine respectively.

Bilateral cervical sympathectomy was performed in 4 rats, 5 days before killing. Decentralization of the right superior cervical ganglion was performed in three rabbits by cutting the truncus sympathicus a few cm below the ganglion. These rabbits were killed 2 days after operation, having been reserpinized 4 hours before killing with a dose of 5 mg/kg.

The nasal mucosa with the inferior concha of the normal, reserpinized, and operated animals was dissected, freeze-dried and treated with formaldehyde gas from paraformaldehyde for one hour at 80°C, mainly according to Falck (1962). The paraformaldehyde used had been stored over solutions of sulphuric acid giving a relative air humidity of 50–70% according to the technique of Hamberger, Malmfors & Sachs (1965). Following the histochemical treatment the specimens were embedded *in vacuo* in paraffin (Merck, mpt. +56–58°C). The sections were made 8–10 μ thick and mounted in Entellan. The freeze-drying histochemical, embedding and mounting procedures are described in detail by Dahlström & Fuxe (1964). Fluorescence microscopy and microphotography were also performed according to Dahlström & Fuxe (1964).

RESULTS

An abundant number of intensely green-fluorescent, fine, varicose fibres were found surrounding the blood-vessels. After treatment with a large dose of reserpine (24 hours before killing), which produces a depletion of the noradrenaline stored in the adrenergic nerves, the fluorescence disappeared in all the animals studied. Since the method is in itself highly specific (Falck 1962, Corrodi & Hillarp, 1963, 1964, Dahlström & Fuxe, 1964), and the green fluorescence was localized to fine, varicose fibres with the typical appearance of adrenergic nerve terminals and disappeared on reserpine treatment and after sympathetic denervation, there is no doubt that the fluorescence was due to the presence of noradrenaline in such terminals.

Both the arteries and the arterioles show a dense adrenergic plexus (Figs. 1, 2, 3, 4, and 5). The precapillary vessels (metarterioles) and the venules, however, have only one or two bundles of terminals passing along them. On account of the obvious difficulty in differentiating between pre-

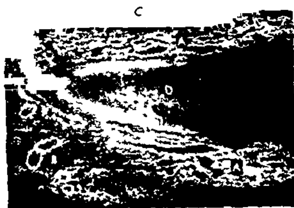


Fig. 1. Inferior concha of normal rabbit. Cross-section. A high amount of green fluorescent material is observed around the wide veins of the erectile tissue (*A*) and around the arteries (*B*). The nasal epithelium is seen at C and the cartilage at *D*. Fluorescence microphotograph. 30 ×.

and postcapillary vessels it cannot be excluded that some of the postcapillary vessels also receive such terminals. The capillaries themselves, on the other hand, do not seem to receive any adrenergic terminals, since practically all of the fluorescent fibres were connected to larger blood vessels.

In all the mammals studied the fluorescence microscopical picture in the nasal mucosa of the inferior concha is dominated by a rich adrenergic plexus surrounding the thin muscle layer of the wide veins (lacunes) of the erectile tissue ("venöse Schwellgewebe") (Figs. 1, 2, 4 and 5). The other parts of the nasal mucosa also have a fairly rich adrenergic innervation of the veins within the tunica propria. The veins receiving the blood



Fig. 2. Inferior concha of normal rabbit. Tangential section. A high amount of green fluorescent material is present surrounding the wide veins of the erectile tissue (*A*) and the arteries (*B*). The nasal epithelium is present at C. Fluorescence microphotograph. 40 ×.

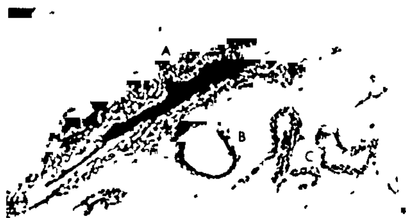


Fig. 3. Inferior concha of normal rabbit. Cross section. A rich plexus of strongly green fluorescent fibres surrounds a vein (A), an artery (B) and certain veins belonging to the erectile tissue (C). Fluorescence microphotograph. 75×

Fig. 4. Inferior concha of normal rabbit. Cross section. A rich plexus of green fluorescent fibres surrounds and is directly superimposed on the muscle layer of arterioles (A) and especially that of the veins of the erectile tissue (B). Some green fluorescent fibres are present within the terminal vascular bed (C) just under the epithelium (D). No green fluorescent fibres surround the glands (E). Fluorescence microphotograph. 100×



Fig 5 Inferior concha of normal rabbit The dense meshwork of green fluorescent fibres surrounding the wide veins of the erectile tissue is illustrated (*A*) The plexus surrounding the artery (*B*) is seen to be directly superimposed on the muscle layer The bundles of terminals building up the plexus have been cross sectioned and appear as fluorescent dots (→) Practically no green-fluorescent fibres are observed surrounding the glands (*C*) Fluorescence microphotograph 160×

from the erectile tissues were surrounded by a dense adrenergic plexus (Fig 3), which equalled that of the arteries

The varicose terminals were found to run in the anastomosing strands of a typical autonomic ground plexus, which in all probability represents the actual innervation apparatus (cf Hillarp, 1946, 1959, Norberg & Hamberger, 1964) Several terminals could be seen to run together in each strand but this was difficult to demonstrate in microphotographs, owing to the fineness and closeness of the terminals The plexus intimately surrounds and lies directly on the muscle layer of the vessels, even in the largest arteries observed (see also Fuxe & Sedvall, 1964, 1965) Practically no terminals were observed to penetrate into the muscle layer

Special attention was paid to the possible occurrence of sphincters with a rich adrenergic innervation, but no differentiated innervation structures could be observed

In the non decentralized rabbits the fluorescent fibres had disappeared after 12 hours of reserpine treatment, whereas after 2 hours' treatment they had remained fairly unchanged After 4 hours of treatment, however, only the fluorescent fibres around the arteries, especially those of the in-

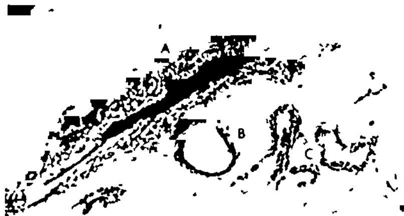


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(cf Carlsson 1965) abolished the fluorescence as did also sympathetic denervation there is no doubt that the nerve fibres demonstrated are true adrenergic terminals containing very high concentrations of the transmitter noradrenaline They have the typical appearance of adrenergic terminals

The very rich adrenergic plexuses surrounding the blood vessels within the nasal mucosa are of the same type as those observed in other tissues (Fuxe & Sedvall 1965 Norberg 1964 Norberg & Hamberger, 1964) There is good evidence that the sympathetic nerves innervating these vessels are vasoconstrictors (cf Malcomson 1959)

It should be pointed out that practically no adrenergic nerve terminals have so far been observed *within* the muscle layer of blood vessels They lie instead directly on the muscle layer The possibility of the muscle cells being excited by the release of noradrenaline from this adrenergic plexus is discussed in papers by Fuxe & Sedvall (1964 1965)

In contrast to the sparse adrenergic innervation of the veins in skeletal muscle (Fuxe & Sedvall 1965) and in most other tissues studied (Norberg & Hamberger 1964), the veins within the nasal mucosa are surrounded by very rich adrenergic plexuses Fairly rich plexuses have been found also around the mesenterial veins (Falck 1962 Norberg & Hamberger, 1964) The blood flow through different regions of the body thus seems to be regulated in different ways depending on the distribution of the adrenergic plexuses over the various sections of the vascular bed In the case of the inferior concha, the very rich adrenergic plexuses around the wide veins of the erectile tissue which have an unusually highly developed innervation apparatus must surely be of high importance in regulating the blood flow

The finding that the adrenergic nerve terminals around the arteries persisted after 4 hours of reserpine treatment while those around the other parts of the vascular bed disappeared is of interest, since it may reflect different impulse flows and/or different turnover rates of the transmitter in these nerves Experiments involving decentralization of the adrenergic terminals to the nasal mucosa before reserpine treatment (4 hours) seem to support this view since in this case not only the arteries but also e g the wide veins of the erectile tissue were seen to be surrounded by fluorescent fibres The effect of decentralization on the action of reserpine has been studied by Hertting Potter & Axelrod (1962) Sedvall (1964) and Fuxe & Sedvall (1964)

ZUSAMMENFASSUNG

Mit Hilfe einer spezifiken und sehr empfindlichen histochemischen Fluoreszenzmethode hat es sich gezeigt dass die Nasenschleimhaut von mehreren Saugetieren eine reichliche adrenergische Nervenversorgung von Arteren Arteriolen und Venen hat aber keine adrenergische Drusennervenversorgung Die Nervenversorgung zu den Venenlakunen in dem venosen Schwellkorper ist besonders reichlich und muss eine grosse Bedeutung fur die Regelung des Blutflusses durch die Nasenschleimhaut haben



Fig. 6. Inferior concha of a rabbit, treated with reserpine (5 mg/kg i.p.) 4 h before killing. The plexus of green fluorescent fibres surrounding the arteries still remains (A) while that surrounding the veins has disappeared (*B*). Fluorescence microphotograph. 120×.

ferior concha, showed a fairly strong fluorescence (Fig. 6), while those in the terminal vascular bed and around the veins (including those of the erectile tissue) had disappeared or showed only a very weak fluorescence.

In the decentralized rabbits, on the other hand, the picture after 4 hours of treatment was different. Fluorescent fibres were observed in all parts of the vascular bed, although with a somewhat reduced intensity.

A dose of 1 mg/kg, 24 hours before killing, abolished the fluorescence in the rabbit, and a dose of 0.2 mg/kg after the same time-period caused a marked decrease in the fluorescence intensity of all the fibres. A dose of 0.05 mg/kg (24 hours before killing) had no effect on the fluorescence microscopical picture.

No adrenergic fibres were present around the glands of the nasal mucosa. The epithelium, however, overlying the inferior concha contained a number of very fine, varicose, adrenergic terminals, present mainly within the basal half of the epithelium.

DISCUSSION

The fluorescence method used shows a high specificity and sensitivity and is based on the principle that under certain conditions primary catecholamines, such as noradrenaline, can be readily converted to intensely fluorescent 6,7-dihydroxy-3,4-dihydroisoquinolines (Falck, Hillarp, Thieme & Torp, 1962; Corrodi & Hillarp, 1963, 1964; Corrodi, Hillarp & Jonsson, 1964). Thanks to this conversion, the presence of the adrenergic transmitter is readily visualized by what in the fluorescence microscope used is a green fluorescence. A detailed description and discussion of the histochemical criteria for the fluorescence reaction have been given earlier (Dahlström & Fuxe, 1964) and extensive studies on the peripheral adrenergic neuron and nerve terminals have been performed in this laboratory (Norberg & Hamberger, 1964). Since the histochemical criteria were satisfied and reserpine treatment, which depletes the transmitter stores in the adrenergic nerves

TONSILLECTOMY CONVALESCENCE

A Clinical Trial

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In a carefully designed clinical trial in 450 patients, the incidence of complications following tonsillectomy and/or adenoidectomy in children was 7½%, and more than one quarter of the patients had a "stormy" convalescence. Prophylactic postoperative Propicillin and Sulphamethoxazole reduced this morbidity, in the latter case, the results being statistically significant. The Propicillin results may have been better if continuous therapeutic blood levels had been attained. No relationship was found between pre-operative bacterial throat flora and complication rate. Despite the likely drug sensitivity incidence of 1%, prophylactic chemotherapy was shown to be indicated following this operation in children.

The objective of this investigation was to ascertain the complication rate following dissection tonsillectomy and/or adenoidectomy in children, and to find out if convalescence was significantly altered by prophylactic chemotherapy.

There were 450 children in the trial, 150 in each of three groups, each child being allotted to his group at random according to a system of random numbers. One third of the patients formed the control group, one third were given the moderately long-acting sulphonamide, SULPHAMETHOXAZOLE ('Gantanol') and one third PROPICILLIN ('Ultrapen"). Sulphamethoxazole was employed in dosage of 250 mg b.d. up to six years of age and 500 mg b.d. over six years of age, for five days commencing twelve hours before operation. Propicillin was used in dosage of 125 mg b.d. up to six years and 250 mg b.d. over six years, again for five days.

The trial extended for one year in order to include the possible seasonal incidence of complications. The children were all admitted to the same open ward of twelve beds, confined to bed for twenty-four hours after operation and, thereafter, allowed to mix in the ward and playroom. Throat swabs were taken from all patients on admission.

The following data were recorded on punch-cards:—Name, Age, Sex, Month of Year, Bed Number, Pre-operative throat flora and sensitivity of the organisms to Sulphamethoxazole and Propicillin, whether tonsillectomy and/or adenoidectomy, complications such as haemorrhage, wound infec-

REFERENCES

CARLSSON, A 1965 Drugs which block the storage of 5-hydroxytryptamine and related amines *Handbuch Exp Pharmacol* (ed V Erspamer), Springer-Verlag Berlin-Gottingen-Heidelberg (In press)

CARLSSON A, FALCK, B and HILLARP N-Å, 1962 Cellular localization of brain monoamines *Acta Physiol Scand* Suppl *196*

CORRODI H and HILLARP, N-Å, 1963 Fluoreszenzmethoden zur histochemischen Sichtbarmachung von Monoaminen 1 Identifizierung der fluoreszierenden Produkte aus Modellversuchen mit 6,7-Dimethoxyisochinolinderivaten und Formaldehyd *Helv Chim Acta 46* 2425

— 1964 Fluoreszenzmethoden zur histochemischen Sichtbarmachung von Monoaminen 2 Identifizierung des fluoreszierenden Produktes aus Dopamin und Formaldehyd *Helv Chim Acta 47*, 911

CORRODI H HILLARP N Å, and JONSSON, G 1964 Fluorescence methods for the histochemical demonstration of monoamines 3 Sodium borohydride reduction of the fluorescent compounds as a specificity test *J Histochem Cytochem* (in press)

DAHLSTRÖM A, and FUXE K, 1964 Existence of monoamine-containing neurons in the central nervous system I Demonstration of monoamines in the cell bodies of brain stem neurons *Acta Physiol Scand 6?* Suppl *232*

FALCK B 1962 Observations on the possibilities of the cellular localization of monoamines by a fluorescence method *Acta Physiol Scand* Suppl *197*

FALCK B Hillarp N-Å, THIEME G and TORP A 1962 Fluorescence of catecholamines and related compounds condensed with formaldehyde *J Histochem Cytochem 10* 348

FUXE K and SEDVALL G, 1964 Histochemical and biochemical observations of the effect of reserpine on noradrenaline storage in vasoconstrictor nerves *Acta Physiol Scand 61* 121

— 1965 The distribution of adrenergic nerve fibres to the blood vessels in skeletal muscle *Acta Physiol Scand* (in press)

HAMBERGER B MALMFORS T and SACHS CH 1965 The standardization of paraformaldehyde and of certain procedures for the histochemical demonstration of certain monoamines *J Histochem Cytochem* (in press)

HAMBERGER B, and NORBERG K A, 1963 Monoamines in sympathetic ganglia studied with a fluorescence method *Experientia 19* 580

HERTTING G POTTER L T, and AXELROD J, 1962 Effect of decentralization and ganglionic blocking agents on the spontaneous release of H³ norepinephrine *J Pharm Pharmacol 136* 289

HILLARP N-Å, 1946 Structure of the synapse and the peripheral innervation apparatus of the autonomic nervous system *Acta Anat* (Basel) Suppl *4*

— 1959 The construction and functional organization of the autonomic innervation apparatus *Acta Physiol Scand* 1959 Suppl *157*

MALCOMSON K G 1959 The vasomotor activity of the nasal mucous membrane *J Laryng 73* 73

NORBERG K A 1964 Adrenergic innervation of the intestinal wall studied by fluorescence microscopy *Int J Neuropharmacol 3* 379

NORBERG K A and HAMBERGER B 1964 The sympathetic adrenergic neuron Some characteristics revealed by histochemical studies on the intraneuronal distribution of the transmitter *Acta Physiol Scand 6?* Suppl *238*

SEDVALL G 1964 Short term effects of reserpine on noradrenaline levels in skeletal muscle *Acta Physiol Scand 6?* 101-108

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In a carefully designed clinical trial in 450 patients the incidence of complications following tonsillectomy and/or adenoidectomy in children was 7 1/2% and more than one quarter of the patients had a "stormy" convalescence. Prophylactic postoperative Propicillin and Sulphamethoxazole reduced this morbidity, in the latter case the results being statistically significant. The Propicillin results may have been better if continuous therapeutic blood levels had been attained. No relationship was found between pre-operative bacterial throat flora and complication rate. Despite the likely drug sensitivity incidence of 1% prophylactic chemo-therapy was shown to be indicated following this operation in children.

The objective of this investigation was to ascertain the complication rate following dissection tonsillectomy and/or adenoidectomy in children and to find out if convalescence was significantly altered by prophylactic chemo-therapy.

There were 450 children in the trial, 150 in each of three groups, each child being allotted to his group at random according to a system of random numbers. One third of the patients formed the control group, one third were given the moderately long acting sulphonamide SULPHAMETHOXAZOLE ("Gantanol") and one third PROPICILLIN ("Ultrapen"). Sulphamethoxazole was employed in dosage of 250 mg. b.d. up to six years of age and 500 mg. b.d. over six years of age for five days commencing twelve hours before operation. Propicillin was used in dosage of 125 mg. b.d. up to six years and 250 mg. b.d. over six years again for five days.

The trial extended for one year in order to include the possible seasonal incidence of complications. The children were all admitted to the same open ward of twelve beds, confined to bed for twenty four hours after operation and thereafter allowed to mix in the ward and playroom. Throat swabs were taken from all patients on admission.

The following data were recorded on punch-cards:—Name, Age, Sex, Month of Year, Bed Number, Pre-operative throat flora and sensitivity of the organisms to Sulphamethoxazole and Propicillin, whether tonsillectomy and/or adenoidectomy, complications such as haemorrhage, wound infec-

tion, otitis media, chest infection, drug sensitivity, etc., and the temperature on each of the six post-operative days. The temperature recordings on the punch cards were made in four groups, viz. (a) less than 99°F, (b) 99–100°F, (c) 100–101°F, (d) over 101°F.

Bacteriology

The throat swabs were taken immediately on admission, the maximum delay being about two hours.

The cultures were made on blood agar plates at 37°C. Paper sensitivity discs were employed using 1.5 micrograms of Propicillin and 200 micrograms of Sulphamethoxazole.

For the purpose of the clinical trial it was considered adequate to record only the predominant colonies grown, except that all colonies commonly considered to be pathogenic in the upper respiratory tract were noted.

Anaesthesia and operative technique

The children were premedicated with Omnopon and Scopolamine according to their weight one hour pre-operatively. Endotracheal intubation was carried out orally with Methohexitone and Suxamethonium and the Endotracheal tube was supported during the operation by means of a Doughty Gag. Anaesthesia was maintained with Fluothane.

The adenoids were curetted with a St. Clair Thomson Curette, the bleeding being allowed to stop spontaneously, and the tonsils removed by the usual dissection method, ligatures being used as required.

RESULTS

The groups compared

On completion of the trial the data were analysed for effectiveness of design. It was found that each group had similar age, sex and nature of operation distributions, that the groups were evenly distributed throughout the months of the year and that each bed in the ward had been used equally by the three groups. There was also a striking group similarity regarding the pre-operative bacterial throat flora and organism sensitivity. It is considered unnecessary to include the tables illustrating these distributions.

85 children had an adenoidectomy alone performed, 29 children tonsillectomy alone, and 336 children had both operations.

Bacteriology

The results of the throat swab cultures are shown in Table 1. The swabs from which the pathogens were cultured also produced non-pathogens. These have been omitted from the table to simplify it. However, almost all of the total number of cultures produced gram negative cocci and other normal throat flora. This is in keeping with the published results of throat swab cultures. 50% of the children had organisms which we have classified as pathogens and 50% had only non-pathogens.

TABLE 1 *Analysis of organisms cultured*

Culture from pre-operative throat swabs	Penicillin	*Sulpho* namide	Control	Total	%
Staph (coagulase positive)	34	32	28	94	20.88
Staph + Haem streptococcus	7	6	8	21	4.66
Staph + Pneumococcus	1	1	1	3	0.66
Staph + H influenzae	1	—	1	2	0.44
Haemolytic streptococcus	21	14	24	59	13.11
Haem streptococcus + Pneumococcus	1	—	—	1	0.22
Haem streptococcus + Haemophilus	—	1	1	2	0.44
Pneumococcus	8	10	7	25	5.55
Pneumococcus + Coliform	1	—	—	1	0.22
Hemophilus influenzae	—	—	2	2	0.44
E coli	—	2	1	3	0.66
Proteus	2	5	3	10	2.22
Total No with pathogens	76	71	76	223	49.55
Streptococcus viridans	16	24	12	52	11.55
Strep viridans + N catarrhalis	14	9	11	34	7.55
N catarrhalis + Diphtheroids	29	37	44	110	24.44
Staph (coagulase negative)	9	2	1	12	2.66
B subtilis	—	—	1	1	0.22
Throat swab sterile	6	7	5	18	4.00
Total No with non pathogens	74	79	74	227	50.42
Total	150	150	150	450	100

TABLE 2 *Analysis of complications*

Complications	No of cases out of 450	% Incidence
Primary haemorrhage	5	1.11
Secondary haemorrhage	11	2.44
Wound infection	17	3.77
Otitis media	1	0.22
Pneumonia	1	0.22
Totals	35	7.77
Temp 100–101°F	109	24.22
Temp > 101°F	21	4.66
Complications or Temp 100° F	124	27.55

Complications

The complications are analysed in Table 2 and their relationship to the pre-operative throat flora is shown in *Table 3* and the relationship to the sensitivity of the organisms to the prophylactic antibiotic of the particular group shown in Table 4 The total *complication* rate proved to be the sur-

TABLE 3. *Throat swab cultures of patients with any complication*

Group	'Pathogens'	"Non pathogens"	Total
Penicillin	22	20	42
Sulphonamide	9	20	29
Control	28	25	53
Total	59	65	124

TABLE 4. *Sensitivity of organisms to prophylactic antibiotic in patients with any complications*

Group	Sensitivity	Resistant	Total
Penicillin	19	23	42
Sulphonamide	15	14	29
Total	34	37	71

prisingly high figure of 7½%. Children who developed complications or who had marked pyrexia, are considered to have had a stormy convalescence. This involved 27% of the children. The complications were fairly evenly distributed throughout the ward and throughout the months of the year.

All the children were seen in the Out-patient Department three to four weeks after discharge from hospital. Several parents commented on minor emotional disturbances, and late complications included one otitis media, one secondary haemorrhage and four cases of bronchitis. These are not included in the table as they did not occur during the trial.

The percentage with complications in the three sub-groups is shown in Table 5. They are not significantly different at the conventional $P = 0.05$ level. A larger series might conceivably produce more significant results.

However, apart from these overt complications, potential complications due to infection and the nature of the convalescence can be assessed from

TABLE 5. *Statistical analysis of data. Percentages of children with complications excluding primary haemorrhage and pyrexia*

Treatment	% with complications	Out of
Control	9.3	150
Sulphonamide	3.3	150
Penicillin	7.3	150

χ^2 (2 D.F.) = 4.48. Not significant at $P = 0.05$ level.

TABLE 6 *Statistical analysis of data Percentages of children with any complications except primary haemorrhage*

Treatment	% with any complications	Out of
Control	35 3	150
Sulphonamide	19 3	150
Penicillin	3 0	150

χ^2 (2 D F) = 9 61

χ^2 (Corrected) for control v Sulphonamide = 8 88 (1 D F)

χ^2 (Corrected) for control v Penicillin = 1 51 (1 D F)

in analysis of complications and the degree of pyrexia present in the post operative period This is illustrated in Table 6

There is thus a significantly smaller percentage of children with any complication in the sulphonamide group than in the control group The percentage in the Penicillin group is smaller though not significantly so

DISCUSSION

Criteria for recommending the operation of tonsillectomy and adenoidectomy were very stringent The children included in this clinical trial therefore cannot be expected to have a normal throat flora 26% had a coagulase positive staphylococcus and 18% haemolytic streptococcus and 40% *either a staphylococcus* a streptococcus or both These proportionally high figures contrast with the very low figures for the Pneumococcus and Haemophilus Influenzae Pneumococci occurred in 7% of the cultures and Haemophilus Influenzae in 2% *The occurrence of 13* pure growths of E *coli and Proteus (3%) appears to be* a recent development in pathological throat swab cultures It should again be emphasised *that the relative* status of these organisms is slightly artificial in that only the predominant organisms are represented

The pathogenicity of the organisms cultured pre operatively was *unrelated* to subsequent complications This was a surprising result and to some might suggest the possibility of cross *infection* with hospital organisms This undoubtedly occurs in a few cases but does not *account for the* vast majority It is much more likely that the complications *are due to the* altered organism host relationship resulting *from the unprotected* faucial and nasopharyngeal wounds permitting *even* the least pathogenic organism the normal throat flora to become *invasive This is further* substantiated by the fact that the complications responded *rapidly* to systemic Penicillin a situation which would be most unlikely *if cross infection* were the basis of the process Again the cultures from the post operative swabs *in compli*

cated cases, produced "normal throat flora" and a few cases with streptococci and staphylococci which were sensitive to penicillin

The high overt complication rate of almost 8% with 27% stormy convalescence behoves us to look for means of reducing it. Here, we confine our argument to prophylaxis with antibiotics. From the overt complications in this series, there is insufficient evidence to be dogmatic but from the results of overt complications and potential complications as evidenced by pyrexia, there is no doubt that prophylaxis improves the post-operative course.

The difference in efficacy between the sulphonamide and the Penicillin prophylaxis is most likely to be due to the blood levels developed following their administration.

Reber *et al.* (1963) calculated the half-life of Sulphamethoxazole at 9–14 hours, placing it with the moderately prolonged acting Sulphonamides. The dosage employed in this trial could be considered therapeutic and must have produced fairly constant blood levels throughout the five days.

By comparison, Morrison & Williamson (1962) showed that orally administered Propicillin and Phenethicillin gave similar peak serum levels at 1 hour with a rapid fall in concentration to 4 hours. Therapeutic blood levels must have been attained only twice in 24 hours with the Propicillin dose used in this trial. Morrison (1961), however, has previously demonstrated the efficiency of this type of regime with Phenethicillin in curing acute suppurative otitis media.

A comparison of the sensitivity of various organisms to Sulphamethoxazole and Propicillin is not called for in a therapeutic trial of this nature, especially as there was no relationship between pre-operative throat flora and post-operative complications and convalescence. Both are effective against the majority of upper respiratory bacteria. It should be noted that Sulphamethoxazole is effective against most strains of E. Coli and Proteus (Holloman *et al.* 1961, Reber *et al.*, 1963).

The difference between Penicillin and Sulphonamide in this trial is thus more apparent than real. The main question, however, is not which antibiotic to use but whether prophylaxis is justifiable at all.

In this series there was no reaction in any of the 150 treated with propicillin but one child out of 150 treated with Sulphamethoxazole developed urticaria and erythema multiforme. Skin sensitivity reactions to Sulphamethoxazole were found by Braden *et al.* in two out of ninety, by Holloman *et al.* (1961) in two out of two hundred and five, by Grater in three out of three hundred and seventy six and by the General Practitioner Research Group in one out of seventy-six. Drug rash in about 1% is therefore to be expected. We encountered no other side effects, but nausea and vomiting, headache and sulphonamide fever might occur. It should be noted that a sensitivity reaction rate of about 1% would be expected with other comparable sulphonamides, with the various penicillins, with tetracyclines and erythromycin.

Crystaluria was considered a possible hazard with Sulphamethoxazole especially in tonsillectomy children who often have to be encouraged to take fluids for the first day or two. In fact we found no evidence of this, nor did Chastain (1962) in 162 children treated with larger dosage.

The question of bacterial superinfection must also be considered. Lourin & Braxton (1963) compared the effect of treating adults with respiratory infection with oral Phenethicillin in doses of 250 mg six hourly and 500 mg six hourly. Therapeutically there was no difference but the bacteriological superinfection rate rose from 3% to 25% with the higher dose. 40% of those developing superinfection incurred clinically detectible *infection*.

Bacteriological superinfection has not been investigated in this clinical trial but the doses employed are sufficiently low to avoid this complication.

There is always reluctance to exhibit antibiotics unless clearly indicated, especially for prophylactic purposes. From the results obtained from this clinical trial, in which the disadvantages of antibiotic administration have *been largely absent*, sufficient evidence is found to justify advocating this type of prophylaxis.

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RESUME

Dans un essai clinique soigneusement réglé de 450 operés l'incidence de com*plications* suivant l'arrachement des amygdales et/ou des adenoides des enfants a été 7½% *et plus* d'un quart des opérés ont eu une « *convalescence orageuse* ». Le Propicillin et Sulphamethoxazole prophylactiques donnés après *l'operation* ont reduit cette morbidite, les resultats dans le *dernier cas* ayant une signification statistique. Les resultats du Propicillin auraient pu *s'ameliorer si l'on* avait parvenu a un niveau therapeutique stable du sang. Nul rapport n'a été trouvé entre la flore bacterienne dans la *gorge avant l'operation* et le nombre proportionnel de complications. Malgre l'incidence *probable de 1%* de susceptibilite a la drogue le traitement prophylactique avec les *drogues semblait* être necessaire suivant cette operation aux enfants.

ZUSAMMENFASSUNG

In einem gründlich *durchgeführten* klinischen Versuch an 450 Patienten traten Komplikationen nach *Tonsillektomie* und/oder Adenoidektomie bei 7½% der Kinder auf und mehr als ein Viertel der Patienten hatte eine stürmische Genesungszeit. Prophylaktisch verabreichtes Propicillin und Sulphamethoxazole setzten die Zahl der Todesfälle *herab*. *Im letzteren* Fall waren die Ergebnisse statistisch bemerkenswert. Die Propicillin-Ergebnisse waren vielleicht besser gewesen, wenn ein gleichbleibender Propicillingehalt im Blut angestrebt worden wäre. Ein Zusammenhang *zwischen* der bakteriellen Rachenflora vor der *Operation* und der Komplikations*rate wurde* nicht gefunden. Eine prophylaktische Chemo

therapie nach dieser Operation and Kindern zeigte sich empfehlenswert trotz eines möglichen Auftretens von Empfindlichkeit gegen das betreffende Medikament von 1%.

REFERENCES

Bradley, B. Colmore, J. P. and Cummings, M. M., 1960: Experience with a new sulfonamide in the treatment of streptococcal pharyngitis. Antimicrol. Agents Ann. 51.

Chastain, P. J., 1962: Use of a new sulfonamide in pediatrics. J. Florida Med. Ass. 48, 810.

General Practitioner Research Group: Report No. 39, 1963: A new sulphonamide. Practitioner 190, 526.

Grater, W. C., 1962: Allergic reactions to oral antibacterials in hypersensitive patients. Ann. Allergy 20, 480.

Holloman, J. L. S., Jr., Ettelson, L. R., Sr., Yergan, C. M., and Barock, I., 1961: Clinical experience with a new sulfonamide sulphamethoxazole. Appl. Ther. 3, 775.

Louria, D. B., and Brayton, R. G., 1963: The efficacy of penicillin regimens. J.A.M.A. 186, 987.

Louria, D. B., and Kaminski, T., 1962: Effects of four antimicrobial drug regimens on sputum superinfection in hospitalised patients. Amer. Rev. Resp. Dis. 85, 649-665.

Morrison, A. W., 1961: Phenethicillin and benzylpenicillin in acute otitis media. Brit. Med. J. 2, 8.

Morrison, J. K., and Williamson, G. M., 1962: Studies with P. A. 248 — A new synthetic penicillin. Chemotherapia (Basel) 5, 15.

Reber, H., Wild, E. and Paris, L.: Experimentelle und klinische Daten über das neue Sulfonamid 5-Methyl-3-Sulfanilamido-isoxazol (RO4-2130). Chemotherapia (Basel) 6, 273.

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MASTOID OSTEOPLASTY WITH ANORGANIC BONE

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The authors have tested the suitability of Ossar® (Liake Oy, Turku Finland) which is a bovine bone treated with ethylenediamine, as a filling substance for bone cavities arising after surgical treatment of chronic otitis The preparation was used in the cases of 47 patients 18 of which had been operated on for cholesteatomatous otitis and 23 for other kinds of chronic otitis 4 had been re operated on for suppurating radical cavities one for chronic mastoiditis and one for adhesive otitis All the patients were subjected to reconstruction of the external auditory meatus according to Palva s method and the empty space remaining behind the musculoperiosteal patch was filled with Ossar® granules Postoperative recovery was uneventful and the results were followed for 6 to 12 months after the treatment None of the ears required re operation due to infection caused by Ossar® as a rule the external auditory meatus retained its shape and no cavities were formed behind the ear In two instances a histological sample of the Ossar® granules was taken postoperatively In the first case a fortnight after the opera tion the tissue resembling granulation tissue and in the second six months after the primary operation the new bone was surrounded with Ossar® granules The authors recommend the method for routine use as the cavity resulting from surgical treatment may be filled with live bone tissue by simple means

In recent years considerable attention has been paid to treatment of the radical cavity in surgery of the middle ear The general course adopted is that the mastoid cavity which forms after an operation is filled and the external auditory meatus is returned to its former shape after surgery

Tauno Palva in the report on his investigation ably describes his method by which the cavity is filled with a musculoperiosteal patch taken from behind the ear and the base of which remains attached to the back of the outer ear Palva attaches the musculoperiosteal patch with Gelfoam

In our experience, the method is reliable, and no particular complications have arisen However occasionally we have observed that a cavity develops behind the ear and sometimes a depression resembling the radical cavity develops at the posterior wall of the external auditory meatus which is liable to putrefy, and requires repeated cleansing Sometimes we have ob served that small serous cavities develop in the area where the muscular patch is situated the cavities were infected and required re-operation

therapie nach dieser Operation und Kindern zeigte sich empfehlenswert, trotz eines möglichen Auftretens von Empfindlichkeit gegen das betreffende Medikament von 1%.

REFERENCES

BRADEN, B., COLMORE, J. P. and CUMMINGS, M. M. 1960. Experience with a new sulfonamide in the treatment of streptococcal pharyngitis. *Antimicrob. Agents Ann.* 55.

CHASTAIN, P. J. 1962. Use of a new sulfonamide in pediatrics. *J. Florida Med. Ass.* 48, 836.

General Practitioner Research Group. Report No. 39. 1963. A new sulphonamide. *Practitioner* 190, 526.

GRATER, W. C. 1962. Allergic reactions to oral antibacterials in hypersensitive patients. *Ann. Allergy* 20, 480.

HOLLOMAN, J. L. S., JR., LEFTHOVE, E. R., SR., YERGAN, C. M. and BABOCK, L. 1961. Clinical experience with a new sulfonamide sulphamethoxazole. *Appl. Ther.* 3, 775.

LOURIA, D. B., and BRAYTON, R. G., 1963. The efficacy of penicillin regimens. *J.A.M.A.* 186, 987.

LOURIA, D. B., and KAMINSKI, T., 1962. Effects of four antimicrobial drug regimens on sputum superinfection in hospitalised patients. *Amer. Rev. Resp. Dis.* 85, 649 (?).

MORRISON, A. W. 1961. Phenethicillin and benzylpenicillin in acute otitis media. *Brit. Med. J.* 2, 8.

MORRISON, J. K. and WILLIAMSON, G. M. 1962. Studies with P.A. 248—A new synthetic penicillin. *Chemotherapia* (Basel), 5, 15.

REBER, H., WILD, E. and PARIS, L. Experimentelle und klinische Daten über das neue Sulfonamid 5-Methyl-3-Sulfonilamido-isoxazol (RO4 2130). *Chemotherapia* (Basel) *C*, 273.

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were discharged from hospital seven days after the operation and were given neomycin cortison ear drops to use until the tympanum had dried by epidermization.

The size of the grains used was 10/20 or 20/40 USP. The grains were AG preparations, i.e. bovine femur head.

MATERIAL

The material described comprises 47 patients with Ossar® ear, operated on between December 1962 and June 1963. The period of observation of those subjected to surgery at a later date is still too short to permit conclusions. The material was chosen at random and divided as follows:

Otitis med. chr. c. cholesteatomate	18
Otitis med. sine cholesteatomate	23
Seq. post operat. radic.	4
Mastoiditis chr.	1
Otitis adhaesiva	1
	4

Twenty one ears were bacteriologically examined. The results are given below.

Staph. aureus	7
Pseudomonas	7
Proteus	5
Klebsiella	3
Staph. albus	2
Escherichia coli	1
Aerobacter aerog.	1

Mixed infection of two bacteria occurred in four patients and of three bacteria in one.

Recovery was normal throughout. No postoperative infections occurred. One or two days after the operation there was a slight accumulation of tissue fluid in the region of the wound in some cases but recovery was spontaneous. Reoperation owing to infection spreading to the Ossar® was not required in a single case. Enlargement of the external auditory meatus was observed in a few instances only; in general the external auditory meatus remained quite normal. No cavities arose behind the ear in the region of the osseous defect.

Re-operation of two ears was required. In the first case the drill slipped in the facial nerve near the foramen stylomastoideum causing a superficial wound in the nerve. At the primary operation the cavity was filled with Ossar® grains without isolating the nerve. The day after the surgical operation peripheral facial paresis occurred. Re-operation of the ear was performed through the former incision 18 days after the primary operation. The facial nerve was liberated from the constriction of the granules and isolated with a strip of Gelfoam. Complete recovery of the nerve was

Filling of the cavity with other kinds of material has been tested. Among these, the following may be mentioned: Acrylene (Mahoney, 1962), bone chips (Schiller & Singer, 1960; Schiller, 1963), cartilage (Guilford, 1960) and free muscular and fascial grafts (Heermann, 1962).

Using the above-mentioned method, only autogenous transplantation of bone will bring about complete obliteration. All other methods result in filling with loose connective tissue, according to Aubrey Schiller. For that reason also Schiller considers that, for cholesteatomous ears, no other material than autogenous bone can be used.

At the Central Hospital of Kuopio we have tested non-organic Ossar® bone, prepared by Lääke Oy, Turku, Finland, for filling of surgical cavities. This preparation consists of bovine bone treated with ethylenediamine and from which the organic substances have been removed as completely as possible, resulting in that its nitrogen content is below 0.05 per cent, but its physical construction has not been changed.

Loose & Hurley (1956) were the first to test ethylenediamine treated bone on dogs, achieving good results. In these experiments, the re-formation of bone was similar to that obtained with the use of auto-transplants. This preparation has since been widely used in dental surgery. Rosomoff *et al.* report good results in man obtained with the use of non-organic bone for filling of cranial cavities resulting from drilling. Hurley *et al.* describe a series of 149 patients in which non-organic bone was used for filling of fractures of the femur, bone deficiency, and fusion of the spinal column. They state that the host bone tolerated non-organic bone well, and ossification occured rapidly.

We have not been able to find any reports on series in which non-organic bone has been used in surgery of the ear, but Wullstein (1963) mentions that he considers it a useful material for filling of the cavity, when required.

In our tests, we have used Ossar® in the following way. Mastoidectomy is carefully performed, all sclerotic bone is removed, also the mucous membrane of the bone cells under the microscope. Reconstruction of the tympanum is done according to well known principles, i.e. preserving the external auditory meatus and using the fascia of the temporal muscle for reconstruction of the ear-drum. The musculoperiosteal patch is placed in the aditus so as to close it and to support the anterior border of the fascia, according to Palva's method. The part of the cavity, caused by operation which the musculoperiosteal patch does not fill is filled with Ossar® structure. A thin disk of Gelfoam, moistened with penicillin solution, is fixed on the surface of the non-organic graft and the wound is closed with mattress sutures. A thin drain is inserted into the wound for a day. A suitable antibiotic powder, for instance, a mixture of sulfa and penicillin may also be blown into the Ossar® structure. To prevent postoperative infection, penicillin and streptomycin may be administered together, provided the bacterial flora of the ear does not require other antibiotics. The patients



Fig 3 Chronic suppuration in ear of twelve year old boy, operated on about a month ago An Ossar® mass is distinctly seen in the sinus-dura corner and in the posterior part of the surgical cavity

achieved in six weeks A histological sample was taken of the granules Macroscopically the granules appeared to be conglomerated into a homogenic mass, resembling loose bone tissue In the microscopical examination, each bone granule was surrounded with connective tissue and in some parts there already occurred reformation of bone tissue It was specially noted that no reaction due to foreign bodies appeared, nor any signs of infection (Fig 1)

In the second case an ear repeatedly operated on in the course of several years owing to recurring infection was concerned At the latest operation, six months ago, Ossar® filling had been used The operation was necessitated due to perilabyrinthine infection which was due to Pseudomonas Surprisingly, no infection of any kind was observed in the region of the Ossar® implantation On the surface of the sinus there were Ossar® granules, but the number of these was markedly decreased Resorption had thus occurred spontaneously In the microscopical examination, the Ossar® granules were surrounded with new bone tissue (Fig 2) Neither infection nor foreign body reaction was observed in this case

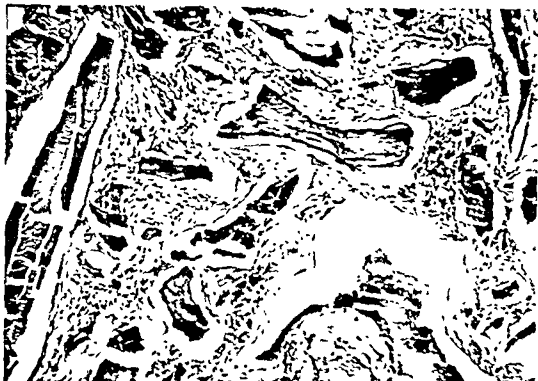


Fig. 1. A fortnight after Ossar® implantation. Ossar® grains mixed with connective tissue of granulation tissue character which is rich in nuclei and partly collagenized. Irregularly angular Ossar® grains are seen in the interstices of the tissue.



Fig. 2. Six months after Ossar® implantation. Collagenous connective tissue and ripened bone tissue are seen in the lower part of the right side of the photograph. Ossar® granules are still visible, especially in the interstices of the bone tissue. The bone tissue is recognized by the sharp angles of the islands.

LOSEE, F. L., and HURLEY, L. A., 1956. Bone treated with ethylendiamine as a successful foundation material in gross species bone grafts. Nature 177, 1032.
— 1956. Successful Gross Species Bone Grafting Accomplished by Removal of the Donor Organic Matrix. Research Report NM 004006.09.01. Naval Medical Research Institute, Bethesda, Maryland.
MAHONEY, J. L., 1962. Tympanoacryloplasty. Arch. Otolaryng. (Chic.) 75, 519.
PALVA, T., 1963. Surgery of chronic ear without cavity. Arch. Otolaryng. (Chic.) 77, 570.
ROSOMOFF, H. L., HURLEY, L. A., and LOSEE, F. L., 1957. Cranial Reconstruction with Ethylendiamine Treated Bone. Research Report NM 710100.06.01. Naval Medical Research Institute, Bethesda, Maryland.
SCHILLER, A., 1963. Mastoid osteoplasty. Arch. Otolaryng. (Chic.) 77, 475.
SCHILLER, A., and SINGER, M., 1960. Mastoid osteoplasty using cancellous autogenous bone: a new procedure. S. Afr. Med. J. 34, 645.
WULLSTEIN, H. L., 1963. Past and future of tympanoplasty. Arch. Otolaryng. (Chic.) 78, 371.

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The X-ray photographs taken after the surgical operation showed that the bone graft was not visible if there was a small amount but the surgical region resembled sclerotic bone. If there was a large amount of Ossar® it was comparatively clearly visible (Fig. 3).

We have concluded on the basis of our experiments that Ossar® is a particularly suitable material for filling of the radical cavity. With the aid of Ossar® the cavity will become filled with normal bone tissue and changes in the shape of bone behind the ear and in the external auditory meatus are avoided. The preparation is easy to handle and it does not prolong the duration of surgery.

Naturally no definite conclusions may yet be drawn as when this paper was written only somewhat more than a year had elapsed since the first operation of this kind was performed. According to Hurley's report Ossar® resorption requires a period of at least 18 months. However, the results of our tests have convinced us of the adequacy of the method and we have adopted it as a routine measure.

ZUSAMMENFASSUNG

Die Verfasser haben die Anwendbarkeit des mit Äthylendiamin behandelten Rindknochens Ossar® (Lake Ox) als Füllungsstoff der Knochenhöhlen untersucht, die in der Chirurgie nach chronischer Otitis entstehen. Das Präparat ist in 47 Fällen angewandt worden, von denen 18 Cholesteatom-Otiten, 23 andere chronische Otiten, 4 früher gemachte eiternde Radikalhöhlohren, eine chronische Mastoiditis und ein Adhaesiv-Otitis waren. In allen Fällen wurde die Rekonstruktion des Gehörganges nach der Methode von Palva gemacht und der leere Raum hinter dem muskuloperiostalischen Läppchen mit den Ossar®-Körnern gefüllt. Die postoperative Genesung war in allen Fällen normal und die Resultate wurden 6-12 Monate nach der Operation überwacht. Es war nicht nötig, die Ohren wegen einer durch Ossar® veranlassten Infektion wieder zu operieren; *der Gehörgang hat im allgemeinen gut seine Form behalten* und hinter dem Ohr ist keine Aushöhlung entstanden. In zwei Fällen wurde ein histologisches Muster der Ossar®-Körner nach der Operation entnommen; in dem einen Fall stellte man schon zwei Wochen nach der Operation fest, dass sich die Höhlen zwischen den Ossar®-Körnern mit einem dem Granulationsgewebe ähnlichen Bindegewebe gefüllt hatten und in dem anderen ... sechs Monate nach der Primäroperation ... waren die Ossar®-Körner von Neuknochen umgeben. Die Verfasser empfehlen die Methode zum Routinegebrauch, weil die Operationshöhlen auf diese Weise durch die einfachen Methoden mit dem lebenden Gewebe gefüllt werden können.

REFERENCES

Clifford, I. R. 1960. C... ... ... fenestration ... *Arch. Otolaryng.* (Chic.) 71: 16.

Hartmann, J. 1960. Experience with free grafts etc. *Z. Laryng. Rhinol. Otol.* 41: 141.

Hurley, L. A., Stinchfield, F. E., Bassett, C. A. L. & Lyon, W. H. 1959. Anorganic Bone Grafting. Research Report NM 11 00 08.03, Naval Medical Institute, Bethesda, Maryland.

1962, 1963) has confirmed the presence of acid phosphatase distributed uniformly throughout the cytoplasm of the secretory cells and has also proved the presence of acetylcholinesterase in both the periacinous nerve net and the acini and of adenosintriphosphatase mainly at the apices of serous cells and in the intracanalicular secretion.

Other sporadic papers report intense esterase activity in the von Ebner's glands towards both α-naphtholacetate and naphthol AS acetate, there being some variability among the various mammalian species examined (Burstone 1956). Nachlas *et al.* (1957) report complete absence of succinic dehydrogenase activity in these glands: the latter observation is the only one concerning oxidation-reduction enzyme activity, while the former report the behaviour of hydrolytic enzymes.

Current cellular biology suggests that the hydrolytic activities which may be demonstrated by cytochemical methods, in particular non-specific phosphatase and esterase activities, have a limited metabolic meaning and may be considered as an approximate index of the total functional state of the organ or, in the case of the glandular structures in question, as an indication of particular properties of their secretions.

Where the enzymatic systems which may be revealed histochemically are concerned, the study of the various dehydrogenases and of other enzyme systems correlated with them in the mitochondrial respiratory chains can be of major importance for elucidation of the metabolic processes of the cell or tissue.

In this paper concerning the cytoenzymological characteristics of the von Ebner's glands particular attention has been paid to the oxidation-reduction activity connected with the tricarboxylic acid cycle (isocitric dehydrogenase, succinic dehydrogenase, malic dehydrogenase) with electron transport (succinic dehydrogenase, diaphorases, cytochrome oxidase) and with hexose monophosphate shunt (glucose-6-phosphate dehydrogenase, TPN diaphorase) and also to activities which, even only indirectly, connect the Krebs cycle with the metabolism of carbohydrates (lactic dehydrogenase) of fats (β-hydroxybutyric dehydrogenase, α-glycerophosphate dehydrogenase) and of proteins (isocitric dehydrogenase, glutamic dehydrogenase). The research has been extended to some hydrolytic activities (acid and alkaline phosphatase, non-specific esterases) and observing from a cytoenzymological standpoint the behaviour of the von Ebner's glands of the rat under various experimental conditions such as extreme senescence, prolonged fasting and physiological or pharmacological stimulation of the secretory processes.

MATERIALS AND METHODS

Samples of tongues of rabbit, dog, guinea pig and rat were taken from the foliatae or circumvallatae papillae of adult male animals killed by decapitation.

CYTOCHEMICAL LOCALIZATION OF OXIDATIVE AND HYDROLYTIC ENZYMES IN VON EBNER'S GLANDS

L. MIRA
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From the Otorhinolaryngological Clinic (Head: Prof. M. Cherubino) and from the Institute of Comparative Anatomy[1] (Head: Prof. M. Vialli) of the University of Pavia

The pattern of several oxidative and hydrolytic enzymatic activities in the serous lingual (von Ebner's) glands has been studied in different mammalian species using cytochemical methods. The results are discussed with respect to metabolic characteristics and possible functional significance of these structures.

In the course of researches on the cytochemical characteristics of certain glandular structures connected with the taste and smell organs, a study was made of enzymatic activity taking place in the serous lingual glands of the basis of the tongue or von Ebner's glands.

This line of research was followed for two reasons. Firstly because of the interesting results which may arise from a dynamic study which may be carried out by application of cytoenzymological techniques, once the structural characteristics of the glands have been defined by cytochemical methods. Secondly because such an analysis may indicate analogies and differences in the metabolic characteristics of the serous lingual glands and the Bowman's glands of the olfactory mucosa, two glandular types which several authors consider to be closely related on account of their possible connection with the peripheral gustatory and olfactory receptors.

However, it should be noted that whereas the Bowman's glands, at least those of the mammalian species as yet examined, are sero-mucous or mixed sero-mucous-serous structures (Mira 1962, Filotto *et al.* 1962), the von Ebner's glands appear to be pure serous structures (Cancello & Sulsenti 1962, Mira 1963).

Enzymatic activity in the olfactory mucosa and its related glands has been widely studied (Baradi & Bourne 1951, 1953, 1959, Burkhardt & Ehrmantraut 1955, Mira 1963) but very little information concerning the serous lingual glands is available. The only relevant data appearing in the literature are those of Baradi & Bourne (1951, 1953) demonstrating the presence of acid phosphatase, esterases and 5-nucleotidase, the latter being found only in the nuclei of the glandular cells.

Further research (Baradi & Bourne 1955, Ellis 1959, Arvy 1959, 1961,

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1962, 1963) has confirmed the presence of acid phosphatase distributed uniformly throughout the cytoplasm of the secretory cells and has also proved the presence of acetylcholinesterase in both the periacinous nerve net and the acini and of adenosintriphosphatase mainly at the apices of serous cells and in the intracanalicular secretion.

Other sporadic papers report intense esterase activity in the von Ebner's glands towards both α naphthol acetate and naphthol AS acetate, there being some variability among the various mammalian species examined (Burstone 1956). Nachlas *et al.* (1957) report complete absence of succinic dehydrogenase activity in these glands: the latter observation is the only one concerning oxidation reduction enzyme activity, while the former report the behaviour of hydrolytic enzymes.

Current cellular biology suggests that the hydrolytic activities which may be demonstrated by cytochemical methods, in particular non specific phosphatase and esterase activities, have a limited metabolic meaning and may be considered as an approximate index of the total functional state of the organ or, in the case of the glandular structures in question, as an indication of particular properties of their secretions.

Where the enzymatic systems which may be revealed histochemically are concerned, the study of the various dehydrogenases and of other enzyme systems correlated with them in the mitochondrial respiratory chains can be of major importance for elucidation of the metabolic processes of the cell or tissue.

In this paper concerning the cytoenzymological characteristics of the von Ebner's glands, particular attention has been paid to the oxidation reduction activity connected with the tricarboxylic acid cycle (isocitric dehydrogenase, succinic dehydrogenase, malic dehydrogenase) with electron transport (succinic dehydrogenase, diaphorases, cytochrome oxidase) and with hexose monophosphate shunt (glucose 6 phosphate dehydrogenase, TPN diaphorase) and also to activities which, even only indirectly, connect the Krebs cycle with the metabolism of carbohydrates (lactic dehydrogenase) of fats (β hydroxybutyric dehydrogenase, α glycerophosphate dehydrogenase) and of proteins (isocitric dehydrogenase, glutamic dehydrogenase). The research has been extended to some hydrolytic activities (acid and alkaline phosphatase, non specific esterases) and observing from a cytoenzymological standpoint the behaviour of the von Ebner's glands of the rat under various experimental conditions such as extreme senescence, prolonged fasting and physiological or pharmacological stimulation of the secretory processes.

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Samples of tongues of rabbit, dog, guinea pig and rat were taken from the foliatae or circumvallatae papillae of adult male animals killed by decapitation.

Normal adult rats (3–4 months old) and rats over 2 years old were examined and in addition rats fasted for 5 to 24 hours or killed 90 minutes or 7 hours after stimulation with pilocarpine sulphate (40 mg/kg intraperitoneally injected).

Immediately after removal the tongue samples were frozen with a jet of carbon dioxide or by immersion in a mixture of propane and isopentane cooled to −170°C with liquid nitrogen and successively placed in a cryostat at −20°C and cut into sections of thickness 7 μ.

The incubation mixtures for the determination of dehydrogenase and diaphorase activity were prepared according to Hess *et al.* (1958) and Scarpelli *et al.* (1958) with some modifications made on the basis of a previous research (Mira 1963), while the method of Burstone (1962) was followed for the cytochrome oxidase and the hydrolases.

The substrates used for acid and alkaline phosphatase and esterases were naphthol AS-BI and AS-MX phosphate and naphthol AS-D acetate (SIGMA) respectively; the diazonium salts Fast Red violet LB and Fast Garnet GBC (G. Gurr) were used as revealers.

The study of each enzymatic activity was accompanied by a control experiment using the incubation mixture without the specific substrate or containing material previously inactivated by heating for 5 minutes in an oven at 100°C.

RESULTS

The results are briefly summarised in Table 1.

The data reported here refer particularly to the von Ebner's glands of the rabbit (see Plates I and II) and almost identical results are obtained for the dog. On the contrary the intensity of reaction is weaker in the guinea pig and still less marked in the rat except where oxidation-reduction enzymes (Krebs's cycle dehydrogenases) are concerned.

Besides this low reactivity in the normal rats used as controls no appreciable variation of enzymatic activity even after alimentary or pilocarpine stimulation, in contrast with behaviour of the major salivary glands, has been noted (Mira & Gerzeli, unpublished results). Even in senile rats enzymatic activity does not seem to be impaired in the active glandular acini, which are however reduced in number by fibrous phenomena and adipose infiltration.

As regards the cytological aspects resulting from the various enzymatic reactions, the oxidation-reduction enzymes give rise to granular precipitates of formazan which reproduce more or less exactly the form and arrangement of the mitochondria. In the serous glandular cells these appear round or rod-like and are often difficult to distinguish because of some diffuse staining of the cytoplasmic background. They are distributed fairly evenly throughout the cellular body but are more dense in the basal portion. In the excretory duct cells the oxidation-reduction activity is more intense and

Table 1 *Intensity*[a] *of enzymatic activity in the secretory cells of von Ebner's glands*

Isocitric dehydrogenase (TPN linked)	+ + +
Succinic dehydrogenase	+ −
Malic dehydrogenase (DPN linked)	+ −
Lactic dehydrogenase	+ + +
Glutamic dehydrogenase (DPN linked)	+
D-β Hydroxybutyric dehydrogenase	+ + +
α Glycerophosphate dehydrogenase	+
Glucose 6 phosphate dehydrogenase	+
TPN diaphorase	+
DPN diaphorase	+ −
Cytochrome oxidase	+ −
Non specific esterases	+ + +
Acid phosphatase	+ +
Alkaline phosphatase	−

[a] The intensity of the enzymatic reaction, evaluated subjectively, varies from − (negative reaction) to + − (weak positive reaction) up to + + + (maximum positive reaction)

the formazan deposits appear as elongated rods, orientated parallely to the main cellular axis

Among the hydrolytic enzymes examined, the esterases and acid phosphatase are strongly positive throughout the cytoplasm of the serous cells, on the other hand alkaline phosphatase is completely absent but appears abundant outside the cells themselves, apparently in connection with the basket cells and the periacinous vascular network

The acini behave uniformly during the various enzymatic reactions studied, without signs of cyclic or parcellar activity of the different components of the serous lingual glands

DISCUSSION

The interpretation of the above data is not simple and it therefore seems worth while to compare the cytoenzymological characteristics of the von Ebner's glands with those of other typical serous glands which are more familiar from this aspect, such as the parotid gland or the pancreas

Such a comparison shows that the intracellular distribution of the enzyme activities under examination is practically the same where hydrolytic and oxidation-reduction enzymes are concerned The latter enzymes are less abundant in the serous secretory cells than in the excretory ducts and this is due to the smaller amount of energy needed for protein synthesis, compared with that required for the active transport of water and ions taking place in the ducts (Walker, 1963)

Normal adult rats (3–4 months old) and rats over 2 years old, were examined, and, in addition, rats fasted for 5 to 24 hours or killed 90 minutes or 7 hours after stimulation with pilocarpine sulphate (40 mg/kg intra peritoneally injected).

Immediately after removal, the tongue samples were frozen with a jet of carbon dioxide or by immersion in a mixture of propane and isopentane cooled to −170°C with liquid nitrogen and successively placed in a cryostat at −20°C and cut into sections of thickness 7 μ.

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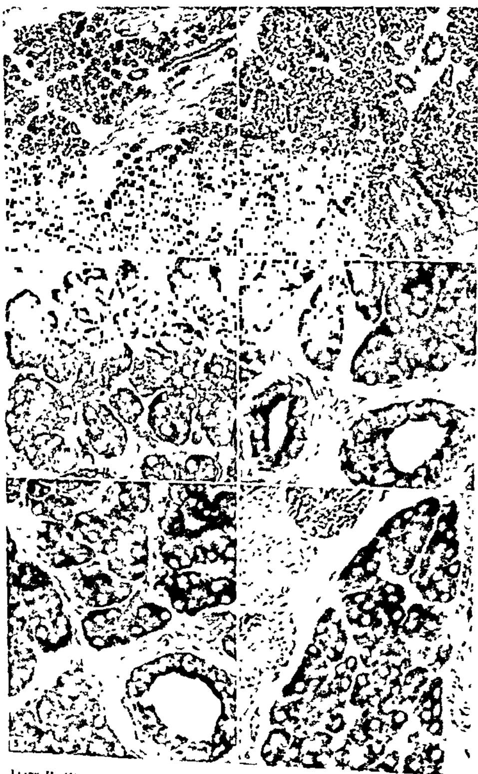


Plate II (1) TPN diaphorase (×132) (2) DPN diaphorase (×132). (3) Non specific esterase (×590) (4) Aeld phosphatase (×590). (3) α Glycerophosphate dehydrogenase (×590) (6) TPN diaphorase (×590).



PLATE I (1) Lactic dehydrogenase (×132) (2) D β Hydroxybutyric dehydrogenase (×132) (3) Isocitric dehydrogenase (×132) (4) Glucose 6 phosphate dehydrogenase (×132) (5) Acid phosphatase (×132) (6) Papilla vallata Lactic dehydrogenase (×132) (7) Excretory duct D β Hydroxybutyric dehydrogenase (×1300)

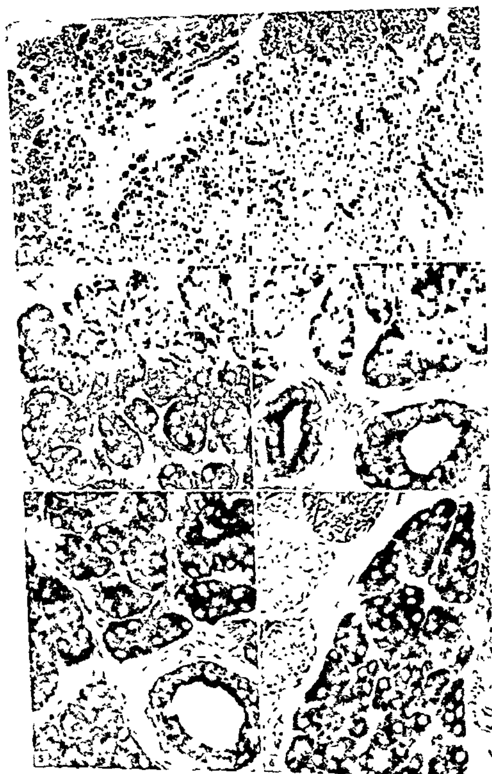


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The behaviour of the various oxidation-reduction activities in the acinous cells is *fairly characteristic*. *In these glands*, contrary to the situation in the pancreas and the major salivary glands, the dehydrogenases connected directly and exclusively with the Krebs cycle (succinic dehydrogenase, malic dehydrogenase) and the enzymes of the respiratory mitochondrial chains (DPN diaphorase, cytochrome oxidase) seem very scarce whereas those involved in other metabolic pathways, especially lactic dehydrogenase and β-hydroxybutyric dehydrogenase, are prevalent.

This could be the result of either an insufficient supply of oxygen to the cell, which would therefore function under relatively anaerobic conditions, or, more probably, an orientation of cellular activity towards particular synthetic processes.

The latter possibility is favoured also by the small but constant positive reaction obtained for enzymes of the pentose cycle and those catalysing single reactions correlated with the metabolism of proteins (glutamic dehydrogenase, isocitric dehydrogenase) or of fats (α-glycerophosphate dehydrogenase) even if the latter cannot be given a definite metabolic significance.

Even more uncertain is the interpretation of the reaction for acid phosphatase and non-specific esterases, it is probable that these activities are connected with the functioning of the lysosomes (Novikoff, 1961) and therefore with the phenomena of pinocytosis and reverse pinocytosis involved in the secretory activity of the cells (Baka, 1962). However, as has already been suggested, it is possible that the intense positive reaction for these enzymes is due to the hydrolytic properties of the secretion from the glands. Particularly relevant to this hypothesis is the observation, made also by Burstone (1956), of esterase activity in the von Ebner's glands which is much more intense than that in morphologically analogous structures such as the serous cells of the parotid or *submaxillary glands*.

CONCLUSIONS

Results prove that the mammalian serous lingual glands are centres of fairly intense metabolic activity, in which synthetic processes related with the specific secretory function predominate.

Of the enzymatic activities investigated, those involved in the pentose cycle and in some stages of protein and fat metabolism are particularly intense while those connected with oxidative reactions and energy-producing processes seem weaker.

The functional characteristics of the glands vary slightly with the various mammalian species examined but without any particular correlation with diet. *In addition, at least in the rat*, these characteristics do not *seem to be* altered markedly at the degree of sensibility of present cytochemical techniques, as a result of physiological or pharmacological stimulation.

Some general conclusions may now be drawn The mammalian von Ebner's and Bowman s glands, as has already been mentioned, were formerly considered to be very similar structures on account of their strict topographical correlation with the peripheral receptors of the two related senses i e taste and smell According to my opinion the two types of glands differ cytochemically and show also differences in their metabolism In the Bowman's glands, contrary to the situation in the serous lingual glands the cytochemically demonstrable Krebs's cycle enzymes seem notably active whereas there is no trace of lactic dehydrogenase activity and very little non specific esterase activity

Further considerations concerning the possible functional significance of the glandular structures in question cannot be sufficiently justified on the basis of this research nor is it possible to relate the activities of the von Ebner s and Bowman's glands with the functions of taste and smell However no histological, physiological or chemical research has as yet unshakeably established such relations

ZUSAMMENFASSUNG

Das Verhalten mehrerer oxydativer und hydrolytischer Enzyme in den serosen Zungendrusen (von Ebnerschen Spuldrusen) von verschiedenen Saugetierarten ist mit histochemischen Methoden studiert worden Die gewonnenen Resultate mit Bezug auf die Merkmale des Stoffwechsels und die mogliche funktionelle Bedeutung dieser Strukturen werden besprochen

REFERENCES

Arvy L., 1959 Contribution a l'etude des chémorecepteurs linguaux chez le mouton domestique *C.R Acad Sci (Par)* *248* 3061

— 1961 Enzymes et appareil gustatif lingual chez le lapin domestique *Ann Biol Animal Biochim Biophys* *1* 145

— 1962 Histochimie des enzymes impliques dans la digestion In A Graumann und K Neumann *Handbuch der Histochemie* vol VII/2 — Enzyme G Fischer Verlag Stuttgart

1963 Comparative histoenzymology of the salivary glands *Ann N Y Acad Sci* *106* 472

Baradi A F., and Bourne G H., 1951 Localization of gustatory and olfactory enzymes in the rabbit and problems of taste and smell *Nature* *168* 977

— 1953 Gustatory and olfactory epithelia *Int Rev Cytol.*, 2 289

1959 Histochemical localization of cholinesterase in gustatory and olfactory epithelia *J Histochem Cytochem* [illegible] 2

Banka T., 1962 Cellular localization of acid phosphatase activity *J Histochem Cytochem* *10* 231

Bourkamp B J [illegible] stochemical studies of the olfactory mucosa of [illegible] 446

Burstone M [illegible] ds *J Histochem Cytochem*, *4* 130

— 1962 *Enzyme Histochemistry* Academic Press, New York and London

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AMICITIAE SACRUM

WÜRZBURG, LE 30 AOUT-4 SEPTEMBRE 1964

CANCILLIO P and SERSENTI G, 1962 Le ghiandole di von Ebner *Riv Patol Clin* 1606

ELLIS R A 1959 Cholinesterases in the mammalian tongue *J Histochem Cytochem* 7 156

ELIOTTO L LAZZARONI A and PIGNATARO O 1962 Contributo allo studio istochimico della mucosa olfattoria *Riv Istoch Norm Pat* 8 263

HESS R SCARPELLI D G, and PEARSE A G E 1958 The cytochemical localization of oxidative enzymes II Pyridine nucleotide linked dehydrogenases *J Biophys Biochem Cytol* 4 753

MIRA E 1962 Caratteristiche istochimiche delle ghiandole di Bowman del coniglio *Boll Mal Orecchio* 80 250

— 1963 Oxidative and hydrolytic enzymes in Bowman's glands *Acta Otolaryng (Stockh)* 56 706

1963 Contributo alla conoscenza istochimica delle ghiandole di von Ebner dei mammiferi *Arch ital Otol* 74 570

NACHLAS M M, TSOU K G, SOUZA E DE, CHANG C S, and SELIGMAN A M, 1957 Cytochemical demonstration of succinic dehydrogenase by the use of a new para nitrophenyl substituted ditetrazole *J Histochem Cytochem* 5 420

NOVIKOFF A B, 1961 Lysosomes and related particles In J Brachet and A E Mirsky *The Cell* Vol II Academic Press New York and London

SCARPELLI D G, HESS R and PEARSE A G E 1958 The cytochemical localization of oxidative enzymes I Diphosphopyridine nucleotide and triphosphopyridine nucleotide diaphorase *J Biophys Biochem Cytol* 4 747

WALKER D G, 1963 A survey of dehydrogenases in various epithelial cells in the rat *J Cell Biol* 17 255

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THE BEGINNING OF OTO-RHINO-LARYNGOLOGY IN WÜRZBURG DURING THE 19TH CENTURY

Paper read during the opening session of the Congress of the Collegium Oto-Rhino-Laryngologicum, 30 Aug. to 3 Sept. 1964 in Würzburg

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Let me acquaint you in a few words with the growth of the Medical and Science Faculties and the rise of Oto-Rhino-Laryngology in Würzburg. The "Juliusspital", which was completed in 1580 and has since then undergone only few alterations, is now probably one of our oldest hospitals, much older, for instance, than the Vienna University Hospital, but it is up to date in its interior construction, and is a good example of a foundation of lasting value, being still wealthy today because of the vineyards and estates left to it by its bishop. It was a University hospital right from the start, for Julius Echter already nominated three Professors of Medicine—one in theoretical medicine, one in practical medicine, and a third in anatomy and surgery.

At the beginning of last century, scientific medicine in Germany began here with the internal specialist Schönlein, who worked from 1817 to 1832 in Würzburg—here he described the Purpura Schönlein—and after that in Zurich and Berlin, a combination of universities which recurs several times in the course of the century.

Kölliker, the great anatomist, spent the whole of his academic life here. He was born in Zurich, where he started as demonstrator in anatomy. In his institute here in Würzburg in 1851 Corti described the organ of hearing which Kölliker was the first to name after him. Besides anatomy and biogeny Kölliker also held lectures in physiology before handing over the latter to Bezold, the discoverer of the Bezold—Jari—Reflex concerning the innervation of the heart, who only reached the age of thirty two years. Bezold's successor was Adolf Fick, who in 1870 announced his principle regarding the estimation of the stroke volume of the heart here in the Society for Physics and Medicine, a society, which we have to mention again in the initial publication of X-rays.

In the vicinity of the University hospital, the "Juliusspital", the medical and scientific foundations were laid. Virchow worked in the same building as Kölliker, in the garden pavilion of the "Juliusspital", built by the Italian Petrini in 1705 for the Prince Bishops, but used as the theatre of anatomy since 1721. Virchow had been Schönlein's pupil and demonstrator in Berlin. While he was studying cytology developed through Schleyden's contributions to phytogenesis in 1838 and Schwann's microscopic investigations of similarity in the structure and growth of animals and plants in 1839, Kölliker, and before him in 1825 Raspail in his paper "Développement de la fécule" had already set up the principle "cell from cell", a principle which Virchow in 1855 extended to the form "omnis cellula e cellula" and applied primarily to pathology. Here in Würzburg he first conceived, expounded and recorded cellular pathology.

After the war of 1866 Würzburg's fortifications were dismantled. Through

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internal specialist, Bergman, the surgeon, and Virchow, who all three co-operated here in the Würzburg Medical Faculty, at that time in the Julius Spital, later—in 1887 in Berlin—took over the treatment of Emperor Frederick, Queen Victoria's son-in-law, involving the famous discussion with Mackenzie. Gerhardt carried out the examination and the biopsy, and Bergman urged the necessity of operating or at least of carrying out a laryngeal fissure, Mackenzie, however, was not convinced that malignity was present and Virchow was unable to demonstrate any carcinoma in the biopsy. There has been much discussion on the question of what consequences this laryngeal carcinoma may have had regarding the outbreak of the First World War, for Emperor Frederick was a Liberal and pro-English in his outlook. Thanks to Gerhardt and his pupil Seifert, laryngology developed very early in Würzburg. In 1883 Seifert opened a rhino-laryngological policlinic, which was joined up with the otological clinic in 1919 by Manasse, who came from Strassburg.

Otological lectures began in Würzburg in 1824, they were conducted by the surgeons Kajetan and Karl Textor up to 1855, after which v. Troltsch began his work in Würzburg in 1856. Kajetan Textor had for instance translated the text book of surgery of Baron Boyer from Paris—11 volumes, one containing only diseases of the nose, the sinuses and the neck, another mostly the ear as to be seen here. Troltsch, as a student, had attended classes here by Kolliker and Virchow (his notes of Virchow's lectures are now housed in the University Library), he then first turned his attention to ophthalmology under Graefe in Berlin and Arlt in Prague, but studied the anatomy of the ear at the same time. A scholarship awarded for voluntary activity during a cholera epidemic *enabled* him to spend some time with Wilde in Dublin and Toynbee in London. And it was on his way back from London in 1855 that Troltsch demonstrated for the first time to the Society of German Physicians in Paris his perforated concave mirror for the illumination of the middle ear. By consistently *evaluating the* results of his new methods of examination he ushered in a new period in the history of otology.

Von Troltsch had not known that this principle of illumination and examination with convergent beams produced by means of a *perforated concave mirror*, had already been thought out and applied by another German doctor, Friedrich Hofmann. In a publication dated 1841—*years before Helmholtz* and Ruete invented their eye mirror—he describes the application of his mirror to the ear, the oral cavity and the nose, and in addition to *rectal and gynaecological* examinations. He anticipated his successors Garcia, Turk and also Troltsch, in that he straightaway recommended an artificial source *of light when using the mirror*. The Würzburg ENT Hospital has the great fortune to possess the original mirrors first used by Hofmann and Troltsch, and which we place on exhibition for you here.

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the work of a Swedish garden architect, the moats and ramparts became the belt of lovely parkland surrounding the city. At the edge of this, very close to the "Juliusspital", there arose new medical and especially scientific institutes and in the second half of the last century exciting scientific activities were carried out in these places. There were such famous researchers as the botanist von Sachs, who in 1868 recognized the significance of chlorophyll and of heliotropism, and the zoologist Boveri, whose studies form the beginning of the chromosome theory of heredity. It was an important period especially in physics and chemistry. Only a few yards from the place where Kölliker, Corti and Virchow worked together was the Institute of Physics, where first Röntgen, then his two immediate successors received the Nobel Prize: Max Wien in 1911 for his work on the absolutely black emitter, a stage on the way to Planck's law of radiation, and Johannes Stark in 1919 for the discovery of the splitting up of spectral lines in an electric field. Other Nobel Prizewinners of these two decades were the chemist Emil von Fischer, later of Berlin, who received it in 1902—the second year in which it was awarded—for his synthesis of glucose and purine bodies resulting in the synthesis of caffeine, and Eduard Buchner, who received the Prize in 1907 for his discovery of cell free enzymatic fermentation by zymases.

Röntgen in 1901 was the first Nobel Prizewinner in physics—the first in medicine at the same time was Behring in Marburg for discovering diphtheria serum. The paper Röntgen published in December 1895 in the Publications of the Society for Physics and Medicine in Würzburg already sets forth in its eight pages everything essential regarding Röntgen rays. On the 21st January 1896 he spoke to the Society on the subject; as a demonstration he completed an X-ray photograph of Kölliker's hand. The meeting was immediately aware of the significance of this discovery, as the minutes of the meeting show—minutes which we show still here in the original. Old Kölliker declared that in 48 years he had never taken part in so momentous a meeting and proposed that these X-rays be called Röntgen rays. An era which was to lead to modern atomic science had begun.

When this so fertile period began in Würzburg, two men began their activity here who carried out decisive work in Oto-Rhino-Laryngology: Karl Gerhardt and Anton von Troltsch. Both these men at this time made available a new method of ascertaining facts, namely examination by means of a mirror. Gerhardt was concerned with examining the larynx, while von Troltsch wished to investigate the middle ear.

Together with Czermak, Gerhardt had attended here in Würzburg Virchow's lectures with their strong clinical emphasis. In 1852 Virchow was even offered the chance of running the Medical Clinic in Zürich. In London in 1855 Garcia had reported to the Royal Society of Medicine on how he had examined his own larynx in a mirror. Türk in Vienna apparently did not know of Garcia's success when he himself in 1857 successfully began to conduct medical examinations of the larynx with the aid of a mirror. Czermak, who began his observations that same year with Türk's mirrors, greatly publicized this novel method; he also informed Gerhardt of it so that the latter was able to investigate the larynx here with Türk's mirrors as early as 1858. He continued these investigations throughout his life and was the first to describe abductor paralysis, which was known in France for a long time as "Syndrome de Gerhardt". Gerhardt, the

internal specialist Bergman the surgeon, and Virchow, who all three co operated here in the Wurzburg Medical Faculty, at that time in the Julius Spital, later—in 1887 in Berlin—took over the treatment of Emperor Frederick, Queen Victoria's son in law, involving the famous discussion with Mackenzie Gerhardt carried out the examination and the biopsy, and Bergman urged the necessity of operating or at least of carrying out a laryngeal fissure, Mackenzie, however, was not convinced that malignity was present and Virchow was unable to demonstrate any carcinoma in the biopsy There has been much discussion on the question of what consequences this laryngeal carcinoma may have had regarding the outbreak of the First World War, for Emperor Frederick was a Liberal and pro English in his outlook Thanks to Gerhardt and his pupil Seifert, laryngology developed very early in Wurzburg In 1883 Seifert opened a rhino laryngological policlinic, which was joined up with the otological clinic in 1919 by Manasse who came from Strassburg

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Universitats Klinik H N O , Wurzburg West Germany

ÉTUDE SUR L'A.D.N.

Son emploi en otologie et dans l'allergie

G. Cambrelin
Bruxelles, Belgique

L'A.D.N., découvert par Avery, a valu à Wilkins, Crick et Watson le Prix Nobel en 1962. L'A.D.N. composante essentielle des gènes qui sont les porteurs du patrimoine héréditaire dans le chromosome. Description d'une cellule avec son A.D.N. et son A.R.N. L'auteur se basant sur l'utilisation de l'A.D.N. comme biocatalyseur dans les cas de sénescence et de déficience organique en préconise l'emploi en otologie et dans l'allergie.

En juillet 1960, lors du Congrès International de la Societas Latina, j'ai évoqué la grande découverte qui venait de se faire. La structure de l'acide désoxyribonucléique (A.D.N.). Celle-ci a valu en 1962 aux savants Wilkins, Crick et Watson le Prix Nobel de Médecine. Francis Perrin avait dit au sujet de cette découverte « Elle offre une voie nouvelle à la compréhension des mécanismes fondamentaux de la matière vivante et s'inscrit dans une évolution très caractéristique de la biologie ».

A ce moment j'envisageais surtout la ferro électricité ou ferro magnétisme de l'A.D.N. que Sadron, Doizon et Polonsky avaient précisé. Jean Rostand s'était également intéressé à la découverte de cette substance.

C'est Avery qui parla le premier en 1944 et identifia l'A.D.N. comme composante essentielle des gènes porteurs essentiels du patrimoine héréditaire dans le chromosome. Ce furent alors les futurs prix Nobel qui en déterminèrent la structure. Une double hélice telle une échelle tordue en escalier dont les montants sont faits en alternance d'un sucre, le désoxyribose, et d'un acide phosphorique, quant aux barreaux de l'échelle ou marches de cet escalier tordu ils sont constitués par des bases organiques aminées de quatre types. L'adénine, la guanine, la thymine et la cytosine.

Chaque barreau est constitué par deux de ces bases réunies par un pont d'hydrogène, mais celles-ci ne peuvent s'unir que 2 à 2. L'adénine avec la thymine, la cytosine avec la guanine.

Il s'agit donc d'un code génétique basé sur quatre éléments. Les 4 bases aminées et dans ce code à quatre lettres serait déterminée la structure des protéines tout au long de la molécule d'A.D.N. Ces protéines sont fabriquées à partir de 20 acides aminés.

Nous savons que l'A.D.N. détermine les caractères héréditaires par l'intermédiaire des protéines qu'il élabore, protéines qui sont plus exactement des enzymes, catalyseurs de toutes les réactions qui sont à la base de toute transformation, de toute synthèse des constituants cellulaires.

saw the publication of Tröltsch's monograph 'Diseases of the Ear', as well as the first and second editions of his 'Textbook of Otology', in 1865 he was appointed professor. As a result of his new methods of examination Tröltsch was able to state his findings accurately and to arrive at a more certain diagnosis; because of this patients flocked to him in great numbers and he had an international practice. But when he was only 48 years old there appeared the first signs of that disease which so tormented him and rendered him so unhappy until his death at the age of sixty. It began with clumsiness in the left hand and other nervous disturbances. It has been assumed that it was a case of multiple sclerosis. Professor Schaltenbrand, our neurological colleague, has been so kind as to check, at my request, Tröltsch's symptoms according to available reports. It was quite obviously a case of Parkinson's Disease following the encephalitis which Tröltsch had already suffered at the age of twenty. This corresponds with Tröltsch's own opinion. In addition to that he had been somewhat hard of hearing since the beginning of his academic teaching career, as a sequence of Otitis media on both sides. Tröltsch suffered greatly as a result of his increasing nervous disturbances and the tremor, pains and alterations in his joints which these produced. His work became more and more difficult for him and he was increasingly forced to cut down his activities, finding it necessary to give up altogether in 1880 at the age of fifty-seven, although in full possession of his mental powers he was later—until his death in 1890—physically completely dependent on the help of others.

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Universitäts-Klinik für H N O, Würzburg, West Germany

ÉTUDE SUR L A D N

Son emploi en otologie et dans l allergie

G CAMBRELIN
Bruxelles Belgique

L A D N découvert par Avery a valu a Wilkins Crick et Watson le Prix Nobel en 1962 L A D N composante essentielle des gènes qui sont les porteurs du patrimoine héréditaire dans le chromosome Description d une cellule avec son A D N et son A R N L auteur se basant sur l utilisation de l A D N comme biocatalyseur dans les cas de senescence et de deficience organique en preconise l emploi en otologie et dans l allergie

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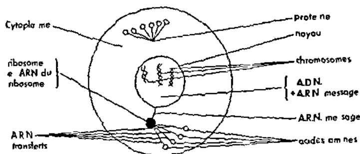


Fig. 1

Les Bactériophages sont des virus dont la tête contient de l'A.D.N. et le fourreau est une protéine. L'A.D.N. pénètre le microbe qui se met à produire des protéines utiles au virus qui alors prolifère. C'est peut-être la production de ces protéines indispensables à la vie du virus dans le microbe que « l'interféron », la nouvelle substance découverte par Isaacs, empêcherait?

Mais il y a une autre explication issue de la découverte du code génétique. On a provoqué sur les virus des mutations, c'est-à-dire des transformations d'un gène en un autre, mutations qui consistent en l'addition ou la suppression d'une base en un endroit quelconque de la molécule d'A.D.N. Ces mutations rencontrent la plupart du temps un résultat remarquable. Le virus ne peut plus infecter la bactérie. Pourquoi? Parceque les lettres du code ont été décalées d'un rang et le virus ne peut plus synthétiser la protéine dont il a besoin.

L'ambition actuelle serait de provoquer des mutations en modifiant l'agencement des porteurs de l'hérédité, c'est-à-dire la disposition des constituants des chromosomes et des germes (spirales et barreaux). C'est l'expérience qui a été réussie une fois sur des canards ayant donné des canards Pékins et des canards khakis.

Enfin disons pour terminer qu'on peut se demander s'il n'existe pas entre les deux spirales des ondes électromagnétiques qui expliqueraient la ferro-électricité ou le ferro-magnétisme que Sadron, Doizon et Polonski ont attribués à l'A.D.N.?

Il nous a paru intéressant de résumer les dernières précisions concernant l'A.D.N. et également l'A.R.N. afin d'en abstraire éventuellement l'utilisation bénéfique en thérapeutique.

Certains laboratoires ont déjà fabriqué quelques spécialités à base d'A.D.N. qui serait extrait de la laitance de poisson. Il paraîtrait donc à conseiller cette substance dans l'alimentation. Un organe qui de tous les organes contient la plus forte proportion d'A.D.N., c'est le thymus, et le thymus de veau, appelé en matière culinaire « ris de veau », en est le plus fourni. En plus le thymus est un des organes qui fabrique le plus d'anti-corps.

Comme l'A.D.N. commande la reproduction de toutes les cellules, il paraît

On sait aujourd'hui depuis moins de deux ans comment s'inscrit sur cette molécule spiralée le message codé qui permet de transmettre les informations héréditaires d'une cellule mère à une cellule fille ; ce patrimoine héréditaire est inscrit sur les filaments du noyau cellulaire baptisés Chromosomes (ils sont 23 paires dans la cellule humaine) et plus exactement sur les granulations de ces filaments appelés gènes.

L'A.R.N. ou acide ribonucléique est un acide nucléique proche de l'A.D.N. mais avec les différences suivantes :

1°) Le désoxyribose est remplacé par un autre sucre, le ribose.

2°) La base aminée thymine y est remplacée par l'uracile.

Au contraire de l'A.D.N. situé dans le noyau, l'A.R.N. est essentiellement dans le cytoplasme et il reste le point de départ de la synthèse des protéines dont la matrice est le ribosome inclus dans le cytoplasme.

C'est l'A.R.N. qui capteraient et véhiculeraient les acides aminés épars dans le cytoplasme et ce vers le ribosome pour former les protéines.

Mais d'où viendrait le point de départ, l'ordre de cette fusion ? Il viendrait évidemment du noyau et de l'A.D.N., mais comment ? Il a été décrit 2 genres d'A.R.N. : l'A.R.N. messager et l'A.R.N. transfert.

L'A.R.N. messager existerait dans le noyau (sans doute fabriqué par l'A.D.N.), en sortirait sous l'action de l'A.D.N. et irait se porter, en se distribuant, sur le ribosome et devenir l'A.R.N. ribosomal qui déclencherait la mise en activité des A.R.N. transferts qui capteraient les acides aminés pour les amener au ribosome et ainsi se ferait la synthèse de la protéine. Il y aurait donc plus exactement trois genres d'A.R.N. : le messager, le ribosomal et le transfert. Cela fait avec l'A.D.N. quatre acides nucléiques.

On peut reproduire schématiquement ainsi ce mécanisme (Fig. 1). Nous avons toujours parlé de protéines ; il eut mieux valu dire les enzymes qui sont des protéines particulières, catalyseurs indispensables à toute réaction biochimique. Ils seraient chez l'homme plusieurs millions d'espèces différentes et ce d'après la disposition des vingt acides aminés qui les composent et surtout d'après celle des quatre acides nucléiques que nous avons cités.

Ces acides nucléiques et les protéines sont deux types fondamentaux de micro-molécules sans lesquelles il n'y a pas de matière vivante sur la planète et vice versa il n'y a pas de protéines et d'acides nucléiques sans matière vivante.

A propos de l'A.R.N. on se demande actuellement si l'A.R.N. messager se contenterait de son rôle de messager ou s'il ne transformerait pas parfois le message de l'A.D.N. ?

Les divers travaux que nous avons résumés opéraient parfois sur des éléments du millionième de micron ; le gène lui-même est d'une taille gigantesque proportionnellement : elle serait d'un micron, certains disent 1/10e de micron ? Le pas de l'hélice d'A.D.N. est de 34 angströms (10 millionièmes de millimètre) et la distance entre les barreaux est de 3,4 angströms.

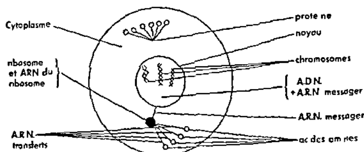


Fig. 1

Les Bactériophages sont des virus dont la tête contient de l'A.D.N. et le fourreau est une protéine. L'A.D.N. pénètre le microbe qui se met à produire des protéines utiles au virus qui alors prolifère. C'est peut-être la production de ces protéines indispensables à la vie du virus dans le microbe que « l'interferon » la nouvelle substance découverte par Isaacs empêcherait?

Mais il y a une autre explication issue de la découverte du code génétique. On a provoqué sur les virus des mutations, c'est-à-dire des transformations d'un gène en un autre, mutations qui consistent en l'addition ou la suppression d'une base en un endroit quelconque de la molécule d'A.D.N. Ces mutations rencontrent la plupart du temps un résultat remarquable. Le virus ne peut plus infecter la bactérie. Pourquoi? Parceque les lettres du code ont été décalées d'un rang et le virus ne peut plus synthétiser la protéine dont il a besoin.

L'ambition actuelle serait de provoquer des mutations en modifiant l'agencement des porteurs de l'hérédité, c'est-à-dire la disposition des constituants des chromosomes et des germes (spirales et barreaux). C'est l'expérience qui a été réussie une fois sur des canards ayant donné des canards Pékins et des canards khakis.

Enfin disons pour terminer qu'on peut se demander s'il n'existe pas entre les deux spirales des ondes électromagnétiques qui expliqueraient la ferro-électricité ou le ferro-magnétisme que Sadron, Doizon et Polonsky ont attribués à l'A.D.N.?

Il nous a paru intéressant de résumer les dernières précisions concernant l'A.D.N. et également l'A.R.N. afin d'en abstraire éventuellement l'utilisation bénéfique en thérapeutique.

Certains laboratoires ont déjà fabriqué quelques spécialités à base d'A.D.N. qui serait extrait de la laitance de poisson. Il paraîtrait donc à conseiller cette substance dans l'alimentation. Un organe qui de tous les organes contient la plus forte proportion d'A.D.N. c'est le thymus et le thymus de veau appelé en matière culinaire « ris de veau » en est le plus fourni. En plus le thymus est un des organes qui fabrique le plus d'anticorps.

Comme l'A.D.N. commande la reproduction de toutes les cellules, il paraît

On sait aujourd'hui depuis moins de deux ans, comment s'inscrit sur cette molécule spiralée le message codé qui permet de transmettre les informations héréditaires d'une cellule mère à une cellule fille, ce patrimoine *héréditaire est inscrit sur les filaments du noyau cellulaire baptisés* Chromosomes (ils sont 23 paires dans la cellule humaine) et plus exactement sur les granulations de ces filaments appelés : gènes

L'A R N. ou acide ribonucléique est un acide nucléique proche de l'A D N mais avec les différences suivantes :

1°) Le desoxyribose est remplacé par un autre sucre, le ribose

2°) La base aminée thymine y est remplacée par l'uracile

Au contraire de l'A D N situé dans le noyau, l'A R N est essentiellement dans le cytoplasme et il reste le point de départ de la synthèse des protéines *dont* la matrice est le ribosome inclus dans le cytoplasme

C'est l'A R N. qui capterait et véhiculerait les acides aminés épars dans le cytoplasme et ce vers le ribosome pour former les protéines

Mais d'où viendrait le point de départ, l'ordre de cette fusion? Il viendrait évidemment du noyau et de l'A D N, mais comment? Il a été décrit 2 genres d'A.R N L'A R N messager et l'A R N transfert

L'A R N messager existerait dans le noyau (sans doute fabriqué par l'A D N), en sortirait sous l'action de l'A D N. et irait se porter, en se détruisant, sur le ribosome et devenu l'A R N ribosomal qui déclencherait la mise en activité des A R N transferts qui capteraient les acides aminés pour les amener au ribosome et ainsi se ferait la synthèse de la protéine Il y aurait donc plus exactement trois genres d'A R N Le messager, le ribosomal et le transfert Cela fait avec l'A D N quatre acides nucléiques

On peut reproduire schématiquement ainsi ce mécanisme (Fig 1) Nous avons toujours parlé de protéines, il eut mieux valu dire les enzymes qui sont des protéines particulières, catalyseurs indispensables à toute réaction biochimique Ils seraient chez l'homme plusieurs millions d'espèces différentes et ce d'après la disposition des vingt acides aminés qui les composent et surtout d'après celle des quatre acides nucléiques que nous avons cités

Ces acides nucléiques et les protéines sont deux types fondamentaux de *macro-molécules sans lesquelles il n'y a pas de matière vivante* sur la planète et vice-versa il n'y a pas de protéines et d'acides nucléiques sans matière vivante

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leve l histone la synthese de l A R N par l A D N est cinq fois superieure histone joue donc *un role inhibiteur sur* une grande partie de l A D N

Dans l epreuve inverse remettons de l histone la synthese de l A R N minue a nouveau

En somme toutes les cellules ont les memes genes mais certaines sont ihibees ou « bloquees » par de l histone

Les chromosomes sont *comme une carte perforce dont* les trous porteurs informations codees representent les genes Eh bien l histone bouche ertains trous

Cependant les cellules germinales n ont pas d histone c'est pourquoi lles ne sont pas differenciees Mais s il n y a pas d histone dans les sperma ozoides il y a pourtant une *autre* proteine *La protamine du germe qui* ait place a l histone de l *embryon* et cette proteine bloque aussi tel ou tel ene

Deja on etend ces connaissances recentes aux cancers Certaines cellules ancereuses contiendraient moins d histone que les cellules saines ce qui expliquerait qu *elles* soient moins *différenciées et de ce fait proliféreraient* sans controle Le cancer serait donc comme un trouble de la regulation chromosomique Or certains cancers presentent un taux d histone reduit?

De la à imaginer qu il suffirait d introduire de l histone dans les noyaux cellulaires pour ramener les chromosomes à une activite plus disciplinee, donc à lutter contre le cancer il n y a qu un pas mais il n est pas encore franchi

II *Genes sans chromosomes ou heredite non chromosomique*

Il existerait des genes non portes par des chromosomes et existant donc, non plus dans le noyau mais libres dans le cytoplasme ils sont appeles plasmogenes et se trouveraient dans les mitochondries

De plus non seulement le cytoplasme mais meme la membrane cellulaire participeraient à l heredite et seraient donc genetiques En effet Ambrose a decrit au microscope electronique des membranes cellulaires auxquelles des ribosomes porteurs d A R N etaient attaches ce qui prouverait que la membrane participerait dans la cellule à la synthèse des proteines

Seulement il ne s agit peut etre que d A R N transfert et non d A R N messager et dans ce cas l A D N ne participerait pas à cette synthese?

SUMMARY

A D N discovered by Amery resulted in the award in 1962 of the Nobel Prize to Wilkins Crick and Watson A D N is an essential composite of genes which are the carriers of the *hereditary factor in the chromosome* The description of a cell with its A D N and its A R N is given The author using as a basis the employment of A D N as a bio catalyst in cases of senescence and of organic deficiency recommends its use in otology and in allergy

logique d'en préconiser l'usage en médecine. En fait il est déjà recommandé comme biocatalyseur dans tous les cas de sénescence, de déficience organique post infectieuse et au cours des convalescences. Dans les cas de processus tumoraux, les traitements radiothérapiques, dans les régimes hypoprotidiques amenant de l'hypoprotéinémie, dans la consolidation des fractures, en un mot dans tous les cas de ralentissement du métabolisme desoxyribonucléique dont dépend la synthèse des protéines et des enzymes endo-cellulaires. De là à en projeter l'usage en otologie (comme d'ailleurs en ophtalmologie) dans les cas de perte prématurée ou non de l'audition.

Depuis un an, j'ai moi-même prescrit l'emploi de cette médication en pareils cas, mais il est évidemment trop tôt pour en attendre et surtout en publier des résultats. Il s'agit en effet d'un traitement à long terme étalé sur plusieurs années.

Il est logique d'espérer que dans les cas de vieillissement des cellules et de carence de celles-ci en A.D.N., un apport substantiel, soit sous forme fraîche (thymus de veau ou laitance de poisson) ce qui est évidemment préférable, soit sous forme de produits fabriqués, puisse aider si pas à récupérer du moins à enrayer une évolution pathologique.

C'est un principe analogue à celui qui consiste à prescrire en otologie et en ophtalmologie de la Vitamine A à haute dose additionnée de Vitamine E (Vitamine de régénérescence).

Mais il est un domaine de la pathologie dans lequel on peut espérer aussi des résultats positifs. C'est l'allergie.

Nous savons que bien des états allergiques sont héréditaires. Il est logique que, puisqu'il s'agit de la constituante essentielle des gènes, s'il y a déficience ou carence ou viciation essentielle de ceux-ci en A.D.N., d'espérer un effet positif par son apport. Même plus, comme de perpétuelles mutations entre les deux rampes constitutives se produisent, celles-ci peuvent amener une heureuse modification.

Toujours est-il que dans les états allergiques comme dans les états de sénescence auditive, je me suis attelé à utiliser ce moyen thérapeutique et en publierai les résultats quand le recul en sera suffisamment long.

ADDENDA A « L'ETUDE SUR L'A.D.N. »

I. *L'histone*

Cette protéine découverte déjà en 1884 par Kessel est restée dans l'ombre jusqu'à tout récemment quand on a découvert qu'elle jouait un rôle inhibiteur sur les gènes.

Toutes les cellules ayant le même nombre de chromosomes et de gènes (on compte 6,6 × 10⁻⁹ milligr. d'A.D.N. pour les cellules du veau, par ex.) il fallait que ceux-ci dégénèrent pour constituer des tissus différents. Cette dégénérescence serait dûe à un phénomène d'inhibition.

On constate que si de la chromatine (matière des chromosomes) on

enlève l histone la synthèse de l A R N par l A D N est cinq fois supérieure L histone joue donc un role inhibiteur sur une grande partie de l A D N

Dans l épreuve inverse remettons de l histone la synthese de l A R N diminue a nouveau

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ZUSAMMENFASSUNG

Die von Amery gefundene A.D.N. hat Wilkins, Crick und Watson 1962 den Nobelpreis eingetragen. Die A.D.N. ist der Hauptbestandteil der Gene, welche die Träger der Vererbung in den Chromosomen sind. Eine Zelle mit ihrer A.D.N. und ihrer A.R.N. wird beschrieben. Der Autor, der sich auf die Anwendung der A.D.N. als Bio-Katalysator im Senium und bei organischer Belastung bezieht, befürwortet ihre Anwendung in der Otologie und in der Allergie.

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THE MECHANISM OF BONE CONDUCTION

An experimental study

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In 58 cats measurements were carried out to obtain a more profound insight into the importance of the external auditory canal, the middle and inner ear constructions in connection with bone conduction. It was found that the inertia of the ossicular chain as well as that of the inner ear fluid are by far the most important components causing bone conduction and that the mobile system of the ear must be considered to consist of at least two loosely coupled units of vibration.

A great deal of research has been done into and much has been written about bone conduction. Rinne (1855), Weber (1834), Schwabach (1885), Politzer (1864), Lucae (1864), von Bezold (1885), Krainz (1926), Barany (1938), Herzog (1926), Ranke (1952), von Bekesy (1932), Kirikae (1959) are some from a long list of well known investigators. As to the components causing bone conduction opinions have come to an agreement in the course of years. Not so, however, where the relative importance of those components is concerned.

Bone conduction components are:

1. Deformation of the bony capsule of the labyrinth.
2. Deformation of the middle ear walls.
3. Inertia of the ossicular chain and the inner ear fluid.
4. Vibration of the mandibula.
5. Vibration of the interior of the skull.
6. Vibration of the air in the middle ear cleft.

Fifty eight cats were used, in which measurements were carried out to obtain a more profound insight into the importance of the external auditory canal, the middle and inner ear constructions in connection with bone conduction. The microphonic potential is used as an indicator of the stimulation of the basilar membrane under the various conditions of the external auditory canal, the eardrum and the middle ear, and thus it will serve as a representation of the sensitivity of bone conduction in those situations. From this we can evaluate the importance of the various elements of the

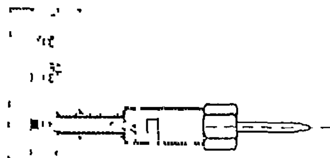


Fig. 1. Vibrator used to set the skull into vibration.

peripheral ear in causing bone conduction. Only the amplitude of the microphonic potential was measured and not the phase, measuring the latter presented too great a number of technical problems.

The skull is set into vibration by a vibrator. A distinctive feature of the vibrator is its driving element which consists of a piezo-electric element. By special provision it sets the skull into vibration with an equal amplitude of acceleration at all frequencies to be used.

The head of the cat is fixed in a ring-shaped sandbag and the vibrator is placed on the mastoid at a certain point near the annulus tympanicus.

The direction of the vibrator axis is such as to acquire an optimum of microphonic potential. Not all cats produce equal amplitudes of microphonic potential with an equal stimulus. To get comparable figures we have indicated, in our curves, the average of the differences between the results in case of an unimpaired cat and after it has been surgically changed: the difference curve.

The microphonic potential is taken off the round window and via filters and amplifiers led to a decibel recorder. The frequency at which the vibrator is operated is changed automatically, so the sensitivity of bone conduction can be measured at all frequencies.

The data obtained have been arranged statistically and have been processed in a computor for which it appeared to be necessary to reduce the number of reference points to those of full and half octaves.

1st experiment (Fig. 4 A)

In 35 cats we have placed a lead ball of 35 mg on the manubrium of the malleus. We find a considerable increase in sensitivity of bone conduction



Fig. 2. The skull is set into vibration with an equal amplitude of acceleration at all frequencies to be used.

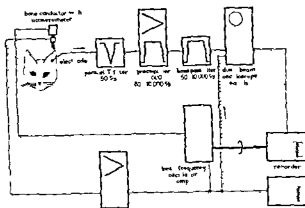


Fig 3 Arrangement of measuring instruments

It is strongest at the low frequencies Kirikae (1959) finds a weaker in crease in sensitivity for the lower frequencies and even a reduction for the high frequencies The reason of it lies, we think, in the fact that his conclusion is based on results from measurements of the movement of the eardrum relatively to the skull and not on the change of the microphonic potential which involves the entire mechanism

With 14 cats we raised the weight to 76 mg and got an identical curve (Fig 4 A)

2nd experiment (Fig 4 B)

In o4 cats the auditory canal is shut off with wax, which does not touch the eardrum We find the sensitivity of bone conduction increased to 2000 cps The explanation of this increased sensitivity does not lie in an increased stiffness that we originally believed to have been brought about by applying the wax but in an increase of the inertia of the eardrum This is so because the cat has no bony auditory canal so the wax presses by way of the membrane wall on the eardrum

Farlier investigators as amongst others Kirikae (1959) also found that by loading the eardrum the threshold of bone conduction is lowered That the mandibula should have any influence here, as was pointed out by von Bekesy in 1932 in similar experiments on humans is not true where the cat is concerned With four cats we have displaced the mandibula but the results did not show any difference It was not likely either, because the cat has not a bony auditory canal

The inertia of the ossicular chain is important to bone conduction, for, when the skull has been set into vibration the ossicles will follow this vibration but out of phase with the skull, by which they set the perilymphe moving relatively to the skull The phase difference between the vibrations of the skull and of the chain arises from the loose connection between chain and skull

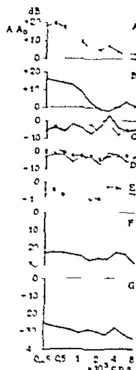


Fig. 4. Summary curve. See text.

3rd experiment (Fig. 4, C)

In order to change the stiffness of the middle ear structure the external membranous auditory canal of nine cats was completely removed after which a metal plate was placed over the eardrum to rest on the annulus tympanicus. Then we affixed this plate with bone-wax on the bone, thus shutting off air-tight the space between plate and eardrum. (The volume between plate and eardrum averages 0.25–0.3 cc.)

Now we find a drop in the sensitivity of the microphonic potential.

4th experiment (Fig. 4, C)

In order to change the stiffness of the ossicular chain even better, with six cats we first removed the external meatus and then spread a thin layer of dental cement across the whole of the eardrum, up to the annulus. The eardrum retained its normal position.

Here too there is a decrease of sensitivity of bone conduction except for *an increase at 3000 cps. However, this increase is statistically not significant.*

5th experiment (Fig. 4, D)

Reduction of stiffness of the eardrum appears to cause a slight loss in sensitivity of bone conduction. With 20 cats smaller and bigger perforations are made in the eardrum. From the following three curves it appears that the size of the perforation apparently does not much matter.

6th experiment (Fig 4, E)

In 34 cats the incus-stapes joint is disconnected "The difference curve" shows a loss in sensitivity of bone conduction So the part of the ossicular chain played in causing bone conduction is of the same order as that of the inner ear Striking are the dips at the 500 and 2000 cps

7th experiment (Fig 4, F)

In 18 cats we fixed the stapes footplates with dental cement so that no air is left between cement and stapes footplate The sensitivity of bone conduction decreases considerably What microphonic potential we find might be caused by a deformation of the labyrinthine capsule So deformation of the capsule is of small importance to bone conduction in case of the intact ear

The effect is the same if, instead of the stapes foot plate, the round window is fixed

8th experiment (Fig 4, G)

In 19 cats both windows are fixed Here too we find a considerable loss in sensitivity of bone conduction It is worth mentioning that cutting the stapedial muscle as was done in all experiments does not show any difference in the present curves

CONCLUSIONS

If we compare the data obtained after fixation of the eardrum with those after fixation of the stapes footplate, they appear to differ greatly If the ossicular chain and the inner ear fluids should be a solid unity, as has been taken for granted up to now, though not explicitly stated, there should be no difference So the mobile system of the ear must be considered to consist of at least two loosely coupled units of vibration (Also in our operations upon the human middle ear we find in normal cases a stapes which is rather mobile relatively to the rest of the chain as well as to the oval window)

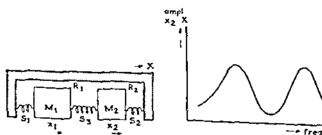


Fig 5 Blockscheme to be taken as a second approach of the mobile system of the middle ear

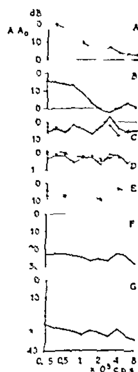


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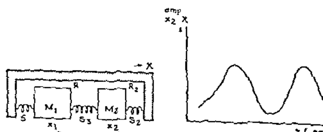


Fig 5 Blockscheme *to be taken* as a second approach of the mobile system of the middle ear

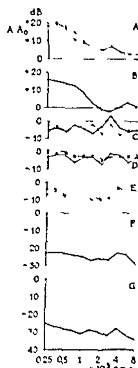


Fig 4 Summary curve See text

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REFERENCES

Békésy G. von 1932 Zur Theorie des Hörens bei der Schallaufnahme durch Knochenleitung *Ann d Physik* *13* 111

Huizinga F H. 1960 Bone conduction The influence of the middle ear *Acta Otolaryng* (Stockh) Suppl *155*

Kirikae I. 1959 An experimental study on the fundamental mechanism of bone conduction *Acta Otolaryng* (Stockh) Suppl *145*

Tonndorf J., and Tabor J R., 1962 Closure of the cochlear windows upon air and bone conduction *Ann Otol*, *71* 50

Tonndorf J., 1963 Quantitative Analyse der Knochenleitung nach Tierversuchen *Arch Ohr Nas Kehlkopfheilk* *18?* 471

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DISCUSSION

J J Groen I want to draw your attention to the similarity between the results of Hoogland and myself on patients with otosclerosis of the round window and Brinkman s results on complete fixation of both windows as compared to a mere fixation of the oval window In the first instance the bone conduction shows a greater loss for the higher frequencies than in the latter situation Otosclerosis of the round window in man shows also the same characteristic of a bone conduction having a loss which increases with frequency at a rate of about 4 dB/octave After Hoogland had removed the obliteration in the round window niche the bone conduction improved at the rate mentioned of 4 dB/octave

W D Keidel A question concerning the phase angle between the cochlear micro phonics and the stimuli because there should be a clear difference in phase angle related to massloading and to elasticity change within the experiments in bone conduction This should allow a distinction between the inertia and the compression theory

W F B Brinkman (Reply) to Prof *Keidel* We did not make any phase measurements

That the vibration units should be comparatively loosely connected is confirmed by the above mentioned dips in 'the difference curve' when the incus-stapes joint is displaced. For displacement of this articulation implies switching from the coupled oscillators to a single one which gives, as is mathematically demonstrable, a figure of at least two dips (Fig. 5).

The blockscheme is therefore to be taken as a second approach of the mobile system of the middle ear. Further conclusions partly mentioned before are:

2. The movement of the mandibula relatively to the external auditory canal is of no importance with cats.
3. Considering the small measurements in regard to the wave lengths of the frequencies used, deformation of the middle and inner ear walls are of no account. Proof of it was given by us for the inner ear.
4. As fixation of the stapes footplate or of the round window does not make any difference, the opening of the perilymphatic duct or other clefts in the perilymphatic space is of no importance.
5. The resonance of the air of the middle ear is, considering the small effect produced by perforating the eardrum, of no importance either.
6. The inertia of the ossicular chain as well as that of the inner ear fluid are by far the most important components causing bone conduction. For the whole range of frequencies considered (250–8000 cps) each of them is equally important. This is contrary to Kirikae's findings who concludes that for the low frequencies only the inertia of the ossicular chain is important, and that for the high frequencies the inertia of the ossicles and of the inner ear fluid and the deformation of the labyrinthine capsule are the most important elements, at least in humans.
7. It is generally true that a change in the middle ear system entails a loss in bone conduction.

RÉSUMÉ

Chez 58 chats on a fait au moyen du dérivé des potentiels microphoniques un examen de l'influence du conduit auditif extérieur et de l'oreille moyenne sur la conduction osseuse. On a trouvé e.a. que l'inertie de la chaîne des osselets et du liquide de l'oreille interne forment les composants les plus importants qui provoquent la conduction osseuse et que le système mouvant de l'oreille consiste au moins en deux unités de vibrations relativement déliées.

ZUSAMMENFASSUNG

Bei 58 Katzen wurde mit Hilfe von Mikrophonpotentialableitungen der Einfluss des äusseren Gehörganges und des Mittelohres auf die Knochenleitung untersucht. Es wurde u.a. gefunden, dass die Trägheit der Gehörknöchelchenkette und der Innenohrflüssigkeit die bedeutendsten Komponenten sind für die Entstehung des Knochenhörens und dass das bewegte System des Ohres aus mindestens zwei voneinander ziemlich unabhängigen Schwingungseinheiten besteht.

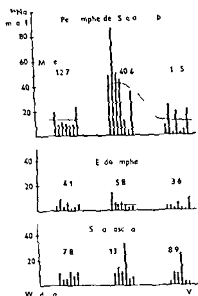


Abb. 1. Na-Gehalt in der Perilymphe der Scala vestibuli, Endolymphe und Stria vascularis nach ²⁴NaCl-Injektion (1 µl) in die Scala vestibuli basalis des Meerschweinchens. Gewinnung der Proben mit Gefriertechnik. Am Injektionsort ist eine Minute später nur noch wenig ²⁴Na vorhanden, wesentlich mehr in der Perilymphe der II. Windung, während in der III. und IV. Windung wenig Na vorliegt, weil wohl nicht alle Perilymphe durch ²⁴NaCl-Lösung ersetzt wurde. Endolymphwerte aller Windungen ungefähr gleich, ebenso die Werte der Stria vascularis.

60 sec ein, so stellen wir fest, daß von der injizierten Menge in der ersten Windung der Scala vestibuli am wenigsten vorliegt, am meisten in der zweiten und mäßig viel in der dritten und vierten Windung (weil die Resorption in die Blutbahnen in der ersten Windung weitaus stärker verläuft als in den übrigen Windungen). In der Endolymphe finden wir in Windung I, II, III und IV ungefähr gleich viel ²⁴Na (Abb. 1).

Man erhält dieselben Resultate, wenn derselbe Versuch unmittelbar nach Ausschaltung des Blutkreislaufes durch Guillotinieren durchgeführt wird, d. h. nach Injektion von 1 µl ²⁴NaCl-Lösung und Einfrieren nach 60 sec. Daraus kann geschlossen werden, daß Natrium durch die Reißnersche Membran in allen Windungen gleich diffundiert, und zwar relativ schwach, wohl auf rein physikalische Weise im Sinne des Konzentrationsgefälles.

II. ⁴²K-Durchtritt durch die Reißnersche Membran

Injizieren wir nun 1 µl ⁴²KCl in isotonischer Lösung in die Scala vestibuli der Basalwindung (wobei zum Druckausgleich stets in der Scala tympani der Basalwindung eine kleine Öffnung gemacht wird), so konstatieren wir nach 60 sec, daß

UNTERSCHIEDE IM METABOLISMUS DER EINZELNEN SCHNECKENWINDUNGEN[1]

A. Meyer zum Gottesberge, S. Rauch und E. Koburg
Düsseldorf, Deutschland

Sowohl anatomisch und biochemisch wie funktionell findet man von Windung zu Windung deutliche quantitative Unterschiede. So fallen die DC-Potentiale der Reissnerschen Membran und der O_2-Verbrauch der Stria vascularis von basal nach apical ab, ebenso die Größe und der Eiweißumsatz der spiralen Ganglienzellen. Die Durchlässigkeit der Reissnerschen-Membran hingegen nimmt von basal nach apical zu. Eine Synopsis der verschiedenen Befunde wird versucht.

Eine der ersten und grundlegenden Entdeckungen der Ohrphysiologie war die Erkenntnis, daß die räumliche Ausdehnung der Schnecke eine Dispersion der ankommenden Schallwellen nach ihrer Frequenz bewirkt. Wellen hoher Frequenzen bilden das Maximum an der Basalwindung, tiefe in der Spitzenwindung aus. Aus neueren Untersuchungen wissen wir aber heute auch mit Sicherheit, daß Wellen tiefer Frequenz, welche die ganze Länge der Schnecke durchlaufen, in allen Windungen zur Erregungsbildung führen, während die Transformation der Schallwellen hoher Frequenz auf die Basalwindung beschränkt ist. Wenn diese Tatsachen feststehen, muß es von Interesse sein, welche morphologischen, biochemischen oder sonstigen Unterschiede zwischen den einzelnen Schneckenwindungen aufzufinden sind. Die Morphologie der Schnecke ist gut erforscht, die Biochemie ist erst „am Werden". Es liegen daher bisher nur vereinzelte Befunde über Unterschiede im Metabolismus der Schneckenwindungen vor.

Über einige Untersuchungen, bei denen sich uns bemerkenswerte Unterschiede im Stoffwechsel einzelner Windungen ergaben, möchten wir hier berichten. Diese Untersuchungen befassen sich mit Permeationsfragen der Reißnerschen Membran, mit der Resorptionsfunktion und dem Sauerstoffverbrauch der Stria vascularis und mit dem Eiweißumsatz der Ganglienzellen. Sie wurden ursprünglich nicht zu dem Zwecke unternommen, Stoffwechselunterschiede aufzuzeigen, vielmehr ergaben sich die Befunde zum großen Teil im Verlauf anderer Untersuchungen.

I. ^{24}Na-Durchtritt durch die Reißnersche Membran

Spritzen wir 1 μl einer isotonischen ^{24}NaCl-Lösung in die Scala vestibuli und frieren die Cochlea in situ (am narkotisierten Meerschweinchen) nach

[1] Die vorliegenden Untersuchungen wurden mit Hilfe der Deutschen Forschungsgemeinschaft durchgeführt.

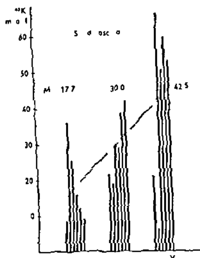


Abb. 4. K-Gehalt der Stria vascularis der verschiedenen Windungen bei Versuch wie Abb. 2. Der Gehalt von Windung III+IV beträgt mehr als doppelt so viel wie in Windung I.

III. Resorptive Funktion der Stria vascularis

Nach den histologischen Bildern ist nicht eindeutig abzuleiten, ob die Stria vascularis eine sekretorische oder vorwiegend resorptive Funktion innehat; nach den elektronenoptischen Bildern scheinen beide Funktionen vorzuliegen. Experimentell wurde allein bis jetzt die Resorption objektiviert, indem man unter Ausschaltung des Blutkreislaufes (siehe oben) das *Auftreten von* ^{42}K in der Stria vascularis überprüfte. Bei denselben Versuchsbedingungen wie II stellte man fest:

a) daß ^{42}K in relativ großen Mengen resorbiert wird;
b) daß die Resorption in der Basalwindung am schwächsten ist und gegen apikal hin zunimmt (Abb. 4);
c) daß die Intensität dieser Kaliumresorption annähernd parallel der Kaliumdiffusion durch die Reißnersche Membran geht, die auch von basal nach apikal hin ansteigt, und da nach Ausschaltung des Blutkreislaufes keine anderen Wege für eine so schnelle Diffusion offenstehen, dieses Kalium deshalb wohl auch aus der Endolymphe stammt.

^{24}Na wird bei gleichen Versuchsanordnungen in allen Windungen durch die Stria vascularis ungefähr gleich stark rückresorbiert.

IV. Atmungsversuche durch Sauerstoffverbrauchs-Messungen

Bei Atmungsversuchen durch Messung des Sauerstoffverbrauchs mit der kartesischen Tauchermethode fanden wir die höchste Atmung in der Stria vascularis der Basalwindung, die nach apikal hin schwächer wird (von

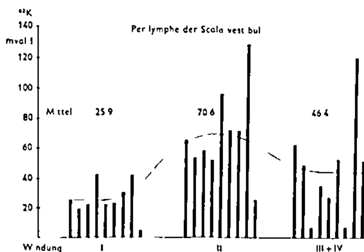


Abb. 2. ^{42}K-Gehalt in der Perilymphe der Scala vestibuli der verschiedenen Windungen eine Minute nach Injektion von 1 μl ^{42}KCl in die Scala vestibuli basalis. Auch hier geringste Werte in der Basalwindung, was auf schnellere Resorption schließen läßt.

1) in der Scala vestibuli ^{42}K deutlich langsamer resorbiert wird als ^{24}Na, obgleich auch hier die Rückresorption in der Basalwindung am stärksten ist (Abb. 2).
2) Da auch hier die Versuche nach Ausschaltung der Blutzirkulation durch Guillotinieren während der folgenden 2 1/2 Minuten praktisch genau gleich verlaufen, werden wir an den Endolymphwerten wieder die Permeation des ^{42}K durch die Reißnersche Membran ermessen können. Dabei ergibt sich:
a) daß in allen Windungen Kalium 2- bis 3fach schneller durchtritt als Natrium,
b) daß die Konzentration an ^{42}K in den obersten Windungen größer ist als in den unteren Windungen, und zwar in der III. und IV. Windung doppelt so hoch wie in der Basalwindung (Abb. 3).

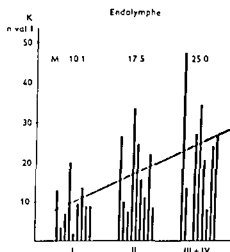


Abb. 3. ^{42}K-Gehalt der Endolymphe der verschiedenen Windungen bei Versuch wie Abb. 2. In Windung III + IV findet sich mehr als doppelt so viel ^{42}K wie in Windung I.

TABELLE 2. *Einbau radioaktivmarkierter Aminosäuren in die Ganglienzellen einzelner Windungen des Ganglion spirale cochleae des Meerschweinchens*

Der Einbau an markierten Aminosäuren ist in der Basalwindung am größten und zur Spitze hin bis zu 30% abfallend

Versuchs-Nr. und Zeit Aminosäure	I. Windung		II. Windung		III. Windung		IV. Windung	
	SKZ	%	SKZ	%	SKZ	%	SKZ	%
Versuch 19 60 Min. H³ Phenylalanin	1024 ±32,0	100	867 ±29,4	85	794 ±28,2	77	768 ±27,7	75
Versuch 3/89 90 Min. H³ Leucin	2387 ±48,8	100	2071 ±45,5	87	1918 ±43,8	80		
Versuch 9/95 90 Min. H³ Lysin	974 ±31,2	100	898 ±29,9	92	804 ±28,3	82		

von Aminosäuren ein Gradmesser des Eiweißstoffwechsels schlechthin ist. Als Nachweismethode der Radioaktivität diente die autoradiographische Methode, über die früher mehrfach berichtet wurde. In den Tabellen 1 und 2 ist die Inkorporation der Aminosäuren in den Ganglienzellen des Ganglion spirale cochleae des Meerschweinchens nach Windungen aufgeteilt dargestellt. Die Absolutwerte stellen Silberkornzahlen (SKZ) über einer Zellfläche von 1120 μ^2 dar, darunter die statistischen Fehler. In der zweiten Spalte finden sich die Relativwerte, wobei die Werte der ersten Windung mit 100 angenommen sind. (Die angegebenen Zeiten beziehen sich auf die Zeit zwischen Injektion der Radioaktivität und der Tötung des Tieres.)

Man erkennt, daß der Einbau radioaktiv markierter Aminosäuren *in der Basalwindung* am größten ist und zur Spitzenwindung hin graduell bis zu 30% absinkt.

Nach Hammer und Trevisi sind die *Ganglienzellen* der Basalwindung größer als die der übrigen Windungen. Bei Analyse der Trockensubstanz fand Hammer in den *Zellen der Basalwindung* einen höheren Proteingehalt.

DISKUSSION

Unsere Befunde zeigen eine meßbare Ortsabhängigkeit der untersuchten Stoffwechselfunktionen von der jeweiligen Windung (mit Ausnahme der Permeationsversuche mit ^{24}Na). Wir fanden, daß die Permeabilität der Reißnerschen Membran und die Resorptionsfähigkeit der Stria vascularis für ^{42}K von der Basis zur Spitze der Schnecke ansteigt. Umgekehrt sind der Sauerstoffverbrauch der Stria vascularis und der dynamische Eiweißumsatz im Ganglion cochleare *in der Basalwindung* wesentlich größer als in der Apikalwindung.

Permeabilität der Reißnerschen Membran und Resorptionsfähigkeit der

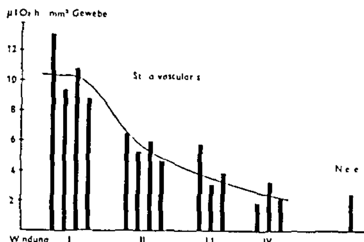


Abb. 5. Sauerstoffverbrauch der Stria vascularis der einzelnen Schneckenwindungen des Meerschweinchens, bestimmt mit der kartesischen Taucher-Methode. Der Sauerstoffverbrauch pro 1 mm³ Gewebe ist in Windung I drei- bis vierfach hoher als in Windung IV.

etwa 11 μl O_2/h fur 1 mm³ Gewebe in der Basalwindung bis zu 3 μl O_2/h mm³ Gewebe in der Apikalwindung) (Abb. 5).

Die Kurve des O_2-Verbrauchs der Stria vascularis verläuft gleich der der DC-Potentiale, d. h. von basal nach apikal hin abfallend.

3. *Eiweißumsatz in den Ganglienzellen des Ganglion cochleare*

Die Versuche wurden an Meerschweinchen ausgeführt, denen radioaktiv markierte Aminosäuren injiziert wurden (^{3}H-Phenylalanin, ^{3}H-Leucin, ^{3}H-Lysin). Da bei der Verwendung verschiedener Aminosäuren praktisch gleiche Einbauraten gemessen wurden, darf man folgern, daß der Einbau

TABELLE 1. *Einbau radioaktivmarkierter Aminosäuren in die Ganglienzellen einzelner Windungen des Ganglion spirale cochleae des Meerschweinchens.*

Der Einbau an markierten Aminosäuren ist in der Basalwindung am größten und zur Spitze hin bis zu 30 % abfallend.

Versuchs-Nr. und Zeit Aminosäure	I. Windung		II. Windung		III. Windung		IV. Windung	
	SKZ	%	SKZ	%	SKZ	%	SKZ	%
Versuch 19 60 Min. H³-Phenylalanin	1021 ±35.2	100	867 ±29.4	85	794 ±26.2	77	768 ±27.7	75
Versuch 20 60 Min. H³-Phenylalanin	879 ±29.6	100	[illegible] ±26.4	79	611 ±24.7	[illegible]	573 ±23.9	65
Versuch 69 60 Min. H³-Phenylalanin	346 ±18.6	100	230 ±15.2	66	199 ±14.1	57		
Versuch [illegible]0 60 Min. H³-Phenylalanin	292 ±17.1	100	255 ±15.9	87	230 ±15.2	79	[illegible]2 ±13.8	66

SUMMARY

In anatomical, biochemical and functional respects there are distinct quantitative differences from one cochlear turn to another. The DC potentials of Reissner's membrane and the oxygen consumption of the vascular stria decrease from the basal to the apical turn. In the same way the size and the rate of protein metabolism of the spiral ganglionic cells decrease. On the other hand the permeability of Reissner's membrane increases from the basal to the apical turn. The various results are synoptically reviewed.

RÉSUMÉ

Les résultats anatomiques, biochimiques et fonctionnels de chaque spire cochléaire sont différents l'un de l'autre. On trouve ainsi une baisse progressive du potentiel DC de la membrane de Reissner et de la consommation d'oxygène de la strie vasculaire de bas vers l'apex, de même une diminution de la grandeur et du métabolisme protéique des cellules ganglionnaires spirales. Par contre les membranes de la rampe moyenne présentent une perméabilité croissante de la base vers le haut. Une vue d'ensemble des différents résultats est envisagée.

LITERATUR

FRIEDMANN, I., 1963: Die Cytologie des Ohres: elektronenmikroskopische Ergebnisse. *Triangel* (Sandoz) *6*: 3.

HAMBERGER, C., 1956: A quantitative cytochemical study of shock wave effects on spiral ganglion cells. *Acta Otolaryng.* (*Stockh.*) Suppl. *127*.

— 1958: On quantitative cytochemical changes in spiral ganglion cells after acoustic trauma. *Acta Otolaryng.* (*Stockh.*) Suppl. *140*: 137.

INATO, S., 1964: Morphologische Aspekte. In: *Biochemie des Hörorgans* (von S. Rauch). Thieme, Stuttgart. S. 17.

KOBURG, E., 1964: Der Eiweißstoffwechsel des Ganglion spirale des Meerschweinchens. *Arch. Ohr.-Nas.-Kehlkopfheilk.* *183* (im Druck).

LAWRENCE, M., WOLSK, D. und LITTON, W. B., 1961: Circulation of the inner ear fluids. *Ann. Otol.* *70*: 753.

RAUCH, S., 1964: *Biochemie des Hörorgans* (herausgegeben von S. Rauch). Thieme, Stuttgart. [*Hier auch weitere Literatur.*]

TREVISI, M., 1959: Rilievi statistici sulla grandezza dei neuroni del ganglio spirale del Corti. *Monit. Zool. Ital.* Suppl. *67*: 477.

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DISCUSSION

S. H. Mygind: Weist auf die großen anatomischen Unterschiede der Sekretions- und Resorptionselemente in der Spitze und in der Basis hin.

G. F. Dohlman: Ich möchte nur fragen, welche von diesen Parametern: Umsatz der Stria vascularis, Permeabilität der Membranen, Sauerstoffumsatz, man mit der v. Bekesyschen Potentialdifferenz zwischen den basalen und apikalen Teilen in Verbindung setzen kann, da dieser Potentialdifferenz eine so große Bedeutung in den Reizhypothesen der Cochlea zugeschrieben worden ist.

A. Meyer zum Gottesberge (Schlußwort): *Dr. Mygind* danke ich für seine interessanten morphologischen Ergänzungen. *Prof. Dohlman* möchte ich antworten, daß wir vermuten, daß der Sauerstoffverbrauch der Stria mit dem Gleichstrompotential zusammenhängt.

Stria vascularis sind beide nur mit der Gefriertechnik nachweisbar, die hier nicht erörtert werden soll. Aus diesem Grund liegen noch keine analogen Befunde von anderen Forschern vor. Daß die Reißnersche Membran jedoch keine inerte Membran ist, geht aus dem relativ hohen Eiweißumsatz dieser Membran hervor, zudem weist die Innenfläche zahlreiche Mikrovilli auf (Lawrence u. Mitarb. 1961; Friedmann, 1963, Iurato, 1964 u. a.). Wir *konnten feststellen, daß Kalium in den oberen Windungen etwa doppelt so schnell die Reißnersche Membran passiert wie in der Basalwindung.* Ob diese Diffusionsvorgänge, die an den Membranen zu Diffusionsvorgängen führen, zu den Gleichstrompotentialen der Cochlea Beziehungen haben, ist ungeklärt. Bemerkenswert ist, daß die Gleichstrompotentiale von basal nach apikal abfallen.

Die Resorptionsfähigkeit der Stria vascularis ist eine experimentell gesicherte Tatsache. Da die Resorption in unserem Versuch von dem Angebot an ^{42}K in der Endolymphe abhängig ist und dieses zufolge der schnelleren Resorption durch die Reißnersche Membran der oberen Windungen hier erhöht angeboten wird, ist nicht bewiesen, daß die Resorptionsfähigkeit der Stria vascularis in den oberen Windungen tatsächlich größer ist. Nur wenn ^{42}K in gleicher Menge in die Scala media verschiedener Windungen diffundiert wäre, wäre die Resorptionsfähigkeit der Stria vascularis sicher zu beurteilen.

Leider dürfte es experimentell äußerst schwierig sein, die Sekretionsfähigkeit der Stria vascularis verschiedener Windungen zu untersuchen, und wir haben bisher Versuche in dieser Richtung nicht unternommen.

Ein sehr interessantes Ergebnis hatten die relativen Messungen des Sauerstoffverbrauchs der Stria vascularis. Der Abfall des O_2-Verbrauchs von basal nach apikal entspricht dem Verlauf des Gleichstrompotentials. Im Sacculus und Utriculus, wo die Stria vascularis fehlt, fehlt auch das Gleichstrompotential, trotz gleichen Elektrolytgehalts wie in der Scala media.

Die Messungen des Sauerstoffverbrauchs der Stria vascularis und des dynamischen Eiweißstoffwechsels der Ganglienzellen weisen auf eine erhöhte Stoffwechselfähigkeit der Basalwindung hin. Von basal nach apikal wird zunehmend weniger Sauerstoff in der Stria verbraucht und weniger Eiweiß in den Ganglienzellen umgesetzt. Das mag verschiedene Ursachen haben. Eine dieser Ursachen erkennen wir, wenn wir die Verteilung der Erregungsbildung in den Schneckenwindungen betrachten. Wie eingangs erwähnt, wird bei Reizung mit verschiedenen Frequenzen die Basalwindung bei allen Frequenzen erregt, die apikale nur bei tiefen Frequenzen. Statistisch betrachtet unterliegt die Basalwindung dabei einer funktionell höheren Belastung und wird im Mittel zu einer höheren Stoffwechseltätigkeit angeregt.

Leider war es uns mit der autoradiographischen Methode nicht möglich, zuverlässige vergleichbare Ergebnisse über den Eiweißumsatz in den Sinneszellen der einzelnen Windungen zu erhalten.

Procedure

Cochlear adaptation was studied in these experiments by comparing the N_1 peak of the whole nerve response, derived from the round window membrane. Figs. 1 and 2 show the response to a single 5000 cps tone pip recorded in this way. During repetitive stimulation with these tone pips the amplitude of the N_1 peak appeared to decrease, just as in the experiments of Derbyshire & Davis (1935) who however used a continuous low frequency tone.

In the experiments described in this paper, series of tone pips were used. After at least a one minute rest the ear of a guinea pig was stimulated by a series of 5 or 6 tone pips each lasting about 2 msec and following each other with an interval of 10 msec. The sound intensity was 60 db re $2 \cdot 10^{-4}$ dyne/cm² (Bruel & Kjaer, Frequency Analyzer type 2105), well below the distortion level of the sound producing apparatus and the middle ear. In this way 5 or 6 N_1 peaks were recorded, of which the first one was unaffected by any previous sound. The action potential responses to the following tone pips decreased in amplitude, which points to a reduction of the number of active neurons in the acoustic nerve during each successive tone pip. This phenomenon is identical with the adaptation as described by Davis (1961) in a general survey about sensory receptor action. The amplitude of the N_2 is decreasing even more than the N_1 under *these circumstances* (Fig. 5), which confirms the observations of Finck & Ruben (1961).

Anesthesia and Operation

Adult guinea pigs were anesthetized by intra muscular injection of 20 mg/kg pernocton and 0.02 mg/kg atropine. Light anesthesia usually ensued in 30 minutes. Adequate surgical anesthesia was performed at that time by inhalation of ether. At the same time 0.1 ml micoren was given to retain sufficient spontaneous respiration. Tracheal cannulation was performed in all cases, since accumulation of mucus *in the nasopharynx* obstructs the airways of the guinea pig often in spite of the atropine.

After careful ligation of the vessels, the bulla tympanica was *approached* ventro-laterally, removing salivary gland, styloid process and the biventer muscle. The bulla was opened with a dental drill. Fig. 3 *shows the topography* of the guinea pig middle ear as encountered in this *approach*. An operation microscope is indispensable, especially when the electrode, *which is a small brush* made of a fine strand of linen thread pinched in a loop of *silver wire*, was *brought* into the niche of the round window. The indifferent electrode was a plate of silver sewed *under the skin* of the neck.

A Philips PH 7 miniature telephone receiver was sewed [illegible]

... [illegible] respiration causes depression of the

THE SIGNIFICANCE OF THE OLIVO-COCHLEAR BUNDLE FOR THE ADAPTATION MECHANISM OF THE INNER EAR

C. C. LIEBBRANDT[1]
Utrecht, The Netherlands

From the Laboratory of Physiology (Head: Prof. J. Jongbloed), State University of Utrecht

Cochlear adaptation was registered by recording the whole-nerve responses of the auditory nerve in the guinea pig to series of tone bursts (60 dB). Decrease of amplitude of the action potential peak (N_1), observed in the course of these series, was abolished by injecting procaine into the internal auditory meatus, thus demonstrating efferent reflex arc activity, normally producing cochlear adaptation.

In audiology much attention is paid to auditory adaptation. Different methods have been used to investigate this phenomenon. Relatively few data, however, have been obtained in animal experiments. Yet only in such experiments the adaptation of the different parts of the auditory system can be studied.

In the present investigation a technique was developed to record the adaptation of the cochlea objectively. The results were similar to earlier observations of Derbyshire & Davis (1935), Hawkins & Kniazuk (1950), Rosenblith (1954), Sørensen (1959), Finck & Ruben (1961), and others. These investigators, however, did not locate the origin of cochlear adaptation. Consequently, in the experiments described in this paper an attempt was made to identify the processes underlying this phenomenon.

The publications of Galambos (1956) and Fex (1962) about the function of the efferent olivo-cochlear bundle described by Rasmussen (1946, 1960) were the starting point for our experiments. The data obtained by these authors suggest the existence of a feed-back circuit, which reflex action suppresses the activity in the cochlea. To evaluate the part of the efferent innervation of the inner ear in the origin of the cochlear adaptation, this phenomenon was studied before and after elimination of the function of the efferent system. Cutting of the middle ear muscles made it possible to differentiate between three possible causes of cochlear adaptation: (1) Contraction of the middle ear muscles, (2) inhibition of the cochlear activity by the central nervous system, and (3) decrease of the cochlear sensitivity, not originated by the central nervous system.

[1] Present address: Dept. of Otolaryngology, State University, Utrecht (Head: Prof. P. G. Gerlings).

Procedure

Cochlear adaptation was studied in these experiments by comparing the N_1 peak of the whole nerve response derived from the round window membrane Figs 1 and 2 show the response to a single 5000 cps tone pip recorded in this way During repetitive stimulation with these tone pips the amplitude of the N_1 peak appeared to decrease just as in the experiments of Derbyshire & Davis (1935) who however used a continuous low frequency tone

In the experiments described in this paper series of tone pips were used After at least a one minute rest the ear of a guinea pig was stimulated by a series of 5 or 6 tone pips each lasting about 2 msec and following each other with an interval of 10 msec The sound intensity was 60 *db re* 2 10⁻⁴ dyne/cm (Bruel & Kjaer Frequency Analyzer type 2105) well below the distortion level of the sound producing apparatus and the middle ear In this way 5 or 6 N_1 peaks were recorded of which the first one was unaffected by any previous sound The action potential responses to the following tone pips decreased in amplitude which points to a reduction of the number of active neurons in the acoustic nerve during each successive tone pip This phenomenon is identical with the adaptation as described by Davis (1961) in a general survey about sensory receptor action The amplitude of the N_2 is decreasing even more than the N_1 under these circumstances (Fig 5) which confirms the observations of *Finck & Ruben* (1961

Anesthesia and Operation

Adult guinea pigs were anesthetized by intra muscular *injection* of 20 mg/kg pernocton and 0 02 mg/kg atropine Light anesthesia usually *ensued in 30* minutes Adequate surgical anesthesia was performed at that time by *inhalation* of ether At the same time 0 1 ml micoren was given to *retain* sufficient spontaneous respiration Tracheal cannulation was performed in all cases since accumulation *of mucus in* the nasopharynx obstructs the airways of the guinea *pig often in spite* of the atropine

After careful ligation of the vessels the bulla *tympanica* was approached ventro laterally removing salivary gland styloid process and the biventer muscle The bulla was opened with a dental *drill Fig 3 shows* the topography of the guinea pig middle ear as encountered in this approach An operation microscope is indispensable especially when the electrode which is a small brush made of a *fine strand* of linen thread pinched in a loop of silver wire was brought into the niche of the round window The indifferent electrode was a *plate of silver* sewed under the skin of the neck

A Philips PH 7 miniature telephone *receiver* was sewed by means of plastic tube of 30

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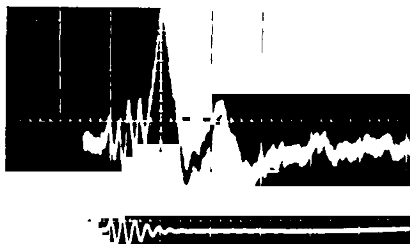


Fig. 1. Short tone burst (lower track), 1 msec/cm. Upper track: cochlear microphonic potential followed by the N_1 and N_2 action potential peak.

cochlear potentials. Electrical heating of the guinea pig was performed in all experiments. During the last preparatory stage the middle ear muscles were cut.

Electronic Apparatus

Stimulation.—The output of a tone generator, producing a tone of 5000 cps, is fed into an electronic device, which interrupts the pure tone. In this way a train of identical tone bursts is produced. The frequency and the duration of the single bursts can be regulated. This signal is fed into a similar apparatus for the second time, which lets pass the train of tone

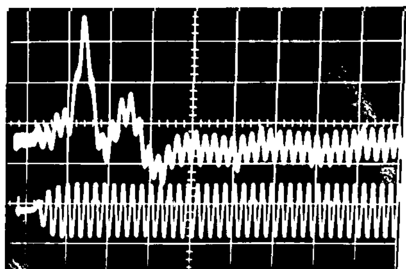


Fig. 2. Longer tone burst (lower track), 1 msec/cm. Upper track: N_1 and N_2 action potential peak superimposed on the cochlear microphonic potential.

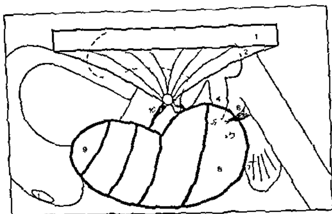


FIG 3 Ventro lateral view of the guinea pig middle ear (left side) 1 annulus tympanicus 2 membrana tympani, 3, malleus, 4, incus, 5, stapes, 6, musculus stapedius 7 niche of the round window, 8 basal turn of the cochlea, 9, apical turn of the cochlea 10 musculus tensor tympani, 11, tuba Eustachii

bursts during 60 msec This happens once a minute The telephone produces each minute in this way a train of 5 or 6 tone bursts The cathode ray oscillograph is triggered at the onset of the train of tone bursts

The upper track (Figs 1 and 2) of the oscillograph picture shows the potentials derived from the round window membrane after appropriate filtering The lower track shows the stimulating tone bursts, as recorded by a microphone with a frequency response identical to the miniature telephone receiver

Recording—In order to obtain a high input-impedance the pre-amplifier is preceded by a low voltage (12 V) cathode follower Especially for recordings in biological experiments a balance pre amplifier was developed by Dr Kylstra A simple transistorized balance circuit provides not only easy and reliable operation, but also high performance in the limited frequency region, which is necessary in this kind of experiments

The cochlear potentials are recorded by means of a two channel cathode-ray oscilloscope (Telequipment D 33), after passing a band-pass filter to eliminate the low frequency electrocardiogram The microphonic potentials (5000 cps) are reduced by the low-pass filter when necessary [1]

Preliminary Tests

To get a reliable recording of the whole-nerve action potentials, the ear was stimulated with *tone pips* Synchronisation of the first action potential volley in the fibres of the acoustic nerve results in a clear action potential peak at the start of the tone burst After the N_1 peak synchronisation is still

[1] More details about the procedure of these experiments have been published in a doctoral thesis about the same subject at the University of Utrecht (Leibbrandt, 1964)

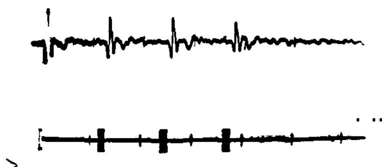


Fig. 4. Response to series of 4 tone bursts. Decrease of the cochlear action potentials (upper track). Lower track: the stimulating tone bursts (10 msec/cm).

present, and a second peak, the N_2, can be recorded. Synchronisation is lost after some milliseconds, and no nervous activity can be detected, when the potentials are recorded from the round window (Figs. 1 and 2). When a low-pass filter is used, the cochlear microphonic potential is reduced, and the action potential remains. To establish the identity of the action potential peaks, a masking effect was employed: a soft hissing sound was made by the observer, and the N_1 and N_2 peaks disappeared, which phenomenon is typical for auditory action potentials.

In the experiments described in this paper it was important to stimulate the ear with tone bursts which produce equal action potential peaks. Therefore the tone bursts were presented to the ear continuously with a repetition rate of about 80 cps.

It appeared that all action potential peaks were equal in this case. This meant that changes of the amplitude of the whole-nerve potentials in the following experiments were due to biological phenomena, and that no accidental changes were involved.

The Adaptation

In order to record cochlear adaptation objectively the ear was stimulated with series of tone bursts.

Previous cutting of the middle ear muscles excluded adaptation by muscular reflex action. As has been described before, each series of tone bursts consisted of 5 or 6 tone pips with a duration of 2 msec, separated by an interval of 10 msec. These series were repeated once a minute usually. In each series a gradual decrease of the amplitude of the N_1 peak of the whole nerve action potential took place (Fig. 4). This phenomenon ap-

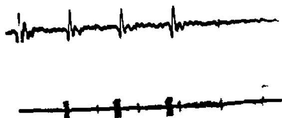


Fig 5 Response to the same tone bursts after injection of procaine in the acoustic nerve Upper track no adaptation is visible in cochlear action potentials Lower track the stimulating tone bursts (10 msec/cm)

peared during stimulation with rather low sound intensities (60 db) The recovery was complete within a minute These qualities are characteristic features of the process of adaptation (Harris & Rawnsley 1953)

In some experiments the duration of the adaptation recorded in this way was determined It appeared that after 75 100 msec the decrease of the amplitude of the N_1 stopped This time corresponds with the data obtained by Derbyshire & Davis (1935) who recorded this fast adaptation but did not describe it Sørensen (1959) demonstrated the same time course as well Obviously they recorded the same part of the adaptation process as we did in our experiments

The adaptation recorded in the experiments described in this paper must be caused either by a process in the cochlea itself or by inhibitory action of the central nervous system upon the cochlea In the second case the efferent innervation of the cochlea is part of an inhibitory cochleo cochlear reflex According to the work of Rasmussen (1953 1960) the auditory nerve the oliva accessoria and the olivo cochlear bundle are involved in this reflex The pathway of this reflex had to be interrupted to differentiate between these two possibilities

Elimination of the Action of the Olivo Cochlear Bundle

In 10 animals procaine was injected into the internal auditory meatus after drilling a hole in the base of the skull beside the bulla tympanica just over the internal meatus The conduction in the efferent and the afferent fibres in the eighth nerve was interrupted in this way

The cochlear microphonic and the whole nerve action potential appeared to be unaltered when the ear was stimulated with single tone bursts (Fisch

& Ruben 1962). When series of tone bursts were presented the adaptation was absent however. This phenomenon was observed in 6 of the 10 animals (Fig. 5). In the other guinea pigs arrest of the respiration occurred or the adaptation remained unchanged. In these cases the procaine was injected into the wrong place probably.

The disappearance of the cochlear adaptation after interruption of the olivo-cochlear bundle indicates that at least a part of the adaptation process of the inner ear is caused by inhibitory reflex action of the central nervous system.

The foregoing experiments demonstrate the existence of inhibition of the cochlear activity during normal hearing. In audiology the adaptation is known to amount to 30 db (Hood, 1950).

It is difficult to express the adaptation described in this paper, in decibels, the relation between action potential amplitude and sound intensity being nonlinear (Davis 1958). According to the amplitude decrease of the action potentials in our experiments the adaptation of the peripheral organ under the influence of the efferent activity of the central nervous system seems to be of the order of 6 db.

Obviously only a part of the adaptation mechanism is recorded and studied. Efferent innervation of different parts of the central auditory pathway having been described (reviewed by Galambos 1958) adaptation of other parts of the auditory system may be caused by similar reflex action.

ACKNOWLEDGMENT

The author wishes to express his gratitude to Prof. Jongbloed for the privilege of working in his laboratory. The assistance of Dr. Kylstra of the same laboratory has been indispensable both in theoretical and in technical problems. The encouragement and assistance of Prof. Gerlings and Mr. Groen of the Otolaryngological Department of this University have been most helpful in the completion of this work.

RÉSUMÉ

Adaptation cochléaire était enregistrée par dérivation des potentiels d'action du nerf auditif intact dans des cobayes à la suite des stimulations des séries de sons discontinus (60 db).

La diminution de l'amplitude des potentiels d'action (N_1) observée dans cettes séries fut supprimée par injection de procaine dans le méat interne, ainsi démontrant l'activité efférente dans le mécanisme de l'adaptation cochléaire.

ZUSAMMENFASSUNG

Adaptation der Schnecke wurde durch Ableitung der Aktionspotentiale des totalen Hörnervs bei Meerschweinchen registriert und zwar während einer Reizung mittels Tonstoss-Serien (60 db).

Die in diesen Serien beobachtete Abnahme der Amplitude der Aktionspotentiale (N_1) konnte durch Procain-Injektion in den inneren Gehörgang beseitigt werden. Damit konnte die efferent hemmende Aktivität im akustischen Reflexbogen nachgewiesen werden, die normalerweise die Adaptation cochleärer Art hervorbringt.

REFERENCES

Davis, H., 1958. Transmission and transduction in the cochlea. *Laryngoscope*, 68, 359.

— 1961. Some principles of sensory receptor action. *Physiol. Rev.*, 41, 391.

Derbyshire, A. J., and Davis, H., 1935. The action potentials of the auditory nerve. *Amer. J. Physiol.*, 113, 476.

Fex, J., 1962. Auditory activity in centrifugal and centripetal cochlear fibres in cat. *Acta Physiol. Scand.*, 55, Suppl. 189.

Finck, A., and Ruben, R. J., 1961. Monaural double click interaction at the round window, eighth nerve and inferior colliculus of cat. *J. Acoust. Soc. Amer.*, 33, 1671.

Fisch, U. P., and Ruben, R. J., 1962. Electrical acoustical response to click stimulation after section of the eighth nerve. *Acta Otolaryng. (Stockh.)*, 54, 532.

Galambos, R., 1956. Suppression of auditory nerve activity by stimulation of efferent fibers to cochlea. *J. Neurophysiol.*, 19, 424.

— 1958. Neural mechanisms in audition. *Laryngoscope*, 68, 388.

Harris, J. D., and Rawnsley, A. I., 1953. Locus of short duration auditory fatigue or adaptation". *J. Exper. Psychol.*, 46, 457.

Hawkins, J. E., and Kniazuk, M., 1950. Recovery of auditory nerve action potentials after masking. *Science*, 111, 567.

Hood, J. D., 1950. Studies in auditory fatigue and adaptation. *Acta Otolaryng. (Stockh.)*, suppl. 92.

Leibbrandt, C. C., 1964. On the auditory adaptation. *Thesis Utrecht.*

Rasmussen, G. L., 1946. The olivary peduncle and other fibre projections of the superior olivary complex. *J. Comp. Neurol.*, 84, 141.

— 1953. Recurrent or "feed back" connections of the auditory system of the cat. *Anat. Rec.*, 115, 361.

— 1960. Efferent fibres of the cochlear nerve and cochlear nucleus. In *Neural Mechanisms of the Auditory and Vestibular Systems*, p. 105. Charles C. Thomas, Springfield, Ill.

Rosenblith, W. A., 1954. Electrical responses from auditory nervous system. *Ann. Otol.*, 63, 839.

Sørensen, H., 1959. Auditory adaptation in nerve action potentials recorded from the cochlea in guinea pigs. *Acta Otolaryng. (Stockh.)*, 50, 438.

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DISCUSSION

M. van Eyck: Je voudrais demander à M. *Leibbrandt* s'il a étudié l'éventuelle protection par la procaïne, des altérations de la fonction cochléaire par les traumatismes sonores.

W. D. Keidel: (1) What happens to the threshold in the Procain series? (2) Did you ever try to watch what happens when you stimulate additionally the contralateral ear recording on the ipsilateral one? (3) What happens to the time-course of adaptation in the Procain series when the oxygen supply is lowered?

M. Portmann: Il semble, d'après les résultats de M. Leibbrandt, que les fibres efférentes interviennent. Nous avons travaillé à Bordeaux ces problèmes de fibres efférentes et je pense que plusieurs phénomènes supposés exclusivement périphériques tel que le recrutement ou l'adaptation pourraient être partiellement centraux. Cette réaction des centres est probablement lente à grande longueur d'onde, effet de sommation peut-être. Le rythme de la stimulation intervient donc. Avez-vous fait varier la fréquence de stimulation et si oui pour quelle fréquence avez-vous trouvé une réponse maxima de cette soi-disant adaptation?

H. Davis: The interpretation of changes in the height of the action potential of the auditory nerve is difficult because it may be greatly affected by changes *in the exact time relations among the impulses in different fibers*. It is possible that the procain has diffused far enough along the nerve to slow the conduction significantly or even block them entirely, particularly the fibers from the first turn. Actually the oscillogram which showed no change in the height of the first spike did show important changes in later parts of the pattern. These suggest a desynchronization of impulses.

I hope that these experiments will continue and will include controls such as surgical section of the efferent tracts in the medulla, electrical stimulation of these fibers and variation of several parameters of the stimulus.

C. C. Leibbrandt (Réponse): à M. *van Eyck*: Pour éviter la fatigue cochléaire des sons traumatisants non pas étaient employés dans ces expériments. Du reste il est peu probable que la diminution de l'adaptation aurait une action protectrice.

to W. D. *Keidel*: (1) Distinct changes of the input-output relation due to procain were not observed. (2) Contralateral stimulation was not performed, a neurally isolated cochlea being studied. (3) Lowering of the oxygen supply causes a rapid decrease of the amplitude of the action potentials, which impedes the recording of the adaptation.

à M. *Portmann*: Le phénomène est indépendant de la fréquence des sons discontinus, il est limité d'un côté par la durée de cette adaptation (75-100 msec) et de l'autre par la période réfractaire du nerf auditif.

to H. *Davis*: Desynchronization of nerve impulses caused by procain would affect the response to each tone burst equally. In that case the adaptation pattern would be visible in the same way, but at a lower level. Actually the amplitude of *the action potential peaks remained nearly unchanged*, while the adaptation disappeared.

DIE BEDEUTUNG DES BINAURALEN HÖRENS FÜR DIE SPRACHLICHE VERSTÄNDIGUNG UNTER LÄRMEINWIRKUNG

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Nach einigen psychoakustischen Versuchen wird durch das binaurale Hören der wirksame Störabstand zwischen Signal und Geräusch wesentlich vergrössert wenn gewisse Parameter (Intensität Laufzeit) bei der Komponenten für beide Ohren verschieden sind Die Wirkung der einzelnen Faktoren wird untersucht (u a Frequenzabhängigkeit Kohärenz) und die Ergebnisse werden im Hinblick auf die zentralnervöse Verarbeitung der binauralen Information diskutiert

In der ohrenärztlichen Praxis sind wir gewohnt Hörprüfungen in einem möglichst ruhigen Raum auszuführen und das hat zweifellos seine guten und berechtigten Gründe Man muß sich aber darüber im Klaren sein daß hierdurch u U ein ganz falsches Bild von der tatsächlichen Leistungsfähigkeit des Organsystems „Gehör entsteht Denn bei dieser Art der Prüfung scheint der einseitig Ertaubte genau so gut zu hören wie der Zweiohrige er versteht ja wie dieser Flüstersprache auf über 6 m

Das gilt aber nur für diese künstlich geschaffene *Prüfungssituation* Unter den akustischen Bedingungen des täglichen Lebens sieht *es u U* ganz anders aus Ihnen allen ist die sogenannte Cocktail Party *Situation* bekannt in einem Raum werden viele Gespräche zur gleichen Zeit geführt und doch ist ein Beobachter in der Lage willkürlich dem einen oder dem anderen Sprecher zuzuhören Der Einohrige kann das nicht mehr sondern die verschiedenen Stimmen vermischen sich für ihn zu einem undurchdringlichen Gewirr

Bekanntlich ist es so daß der *von einer Schallquelle* kommende Schall auf beide Ohren mit einer bestimmten von der *Einfallsrichtung* abhängigen Laufzeitdifferenz und Lautstärkendifferenz auftrifft Dadurch werden wir in die Lage versetzt eine Schallquelle im Raum richtig zu lokalisieren Das ist eine eminent *wichtige Funktion* Doch davon soll hier weniger die Rede sein Ich möchte Ihnen vielmehr über Untersuchungen berichten die eine weniger bekannte aber wohl ebenso *bedeutungsvolle* Leistung des binauralen Hörens aufzeigen nämlich daß *man mit 2 Ohren* bei gleichzeitiger Einwirkung von Störgeräuschen effektiv wesentlich besser hört als mit einem Ohr

Bei den Untersuchungen kam es uns darauf an herauszuarbeiten in welcher Weise die beiden Parameter des binauralen Hörens die interaurale Intensitätsdifferenz und die interaurale Laufzeitdifferenz am Zustandekom

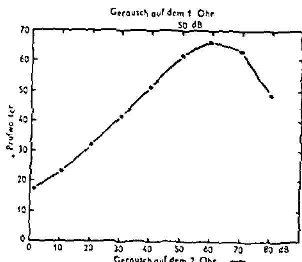


Abb. 1

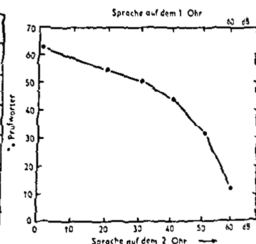


Abb. 2

Abb. 1. Änderung des Sprachverständnisses unter folgenden Versuchsbedingungen: das 1. Ohr erhält Sprache und Geräusch in gleichbleibender Intensität von 50 dB in einem für das Sprachverständnis kritischen Störabstand, sodann wird dasselbe, kohärente Geräusch ohne Sprache auf das 2. Ohr in steigender Intensität gegeben. Mittelwerte von 10 Versuchspersonen.

Abb. 2. Änderung des Sprachverständnisses unter folgenden Versuchsbedingungen: beide Ohren erhalten kohärentes Rauschen von 60 dB Lautstärke. Dem 1. Ohr wird Sprache in gleichbleibender, für das Sprachverständnis kritischer Intensität gegeben, dann wird dem 2. Ohr dieselbe Sprache in steigender Intensität zugeführt, bis derselbe Pegel wie auf dem 1. Ohr erreicht ist. Mittelwerte von 10 Versuchspersonen.

men dieser spezifischen Leistung beteiligt sind. Auf Einzelheiten der Versuchsanordnung kann ich hier leider nicht eingehen, sondern muß mich darauf beschränken, einige der wichtigsten Ergebnisse vorzutragen.

Zunächst haben wir Sprache, d. h. Zahlwörter, über Kopfhörer auf ein Ohr gegeben und gleichzeitig ein weißes Geräusch in einem solchen Intensitätsverhältnis beigemischt, daß nur etwa 20% der Wörter richtig verstanden wurden. Das entspricht also der Situation des Einohrigen, der Sprache bei einem extrem hohen Störpegel zu verstehen sucht. Sodann haben wir dem anderen Ohr dasselbe Geräusch ohne Sprache in steigender Intensität dazugegeben. Die Sprache wird während des ganzen Versuches als von der Seite kommend wahrgenommen. Das Störgeräusch hat zunächst die gleiche scheinbare Einfallsrichtung, verlagert sich aber dann durch Änderung der interauralen Lautstärkenverhältnisse und scheint schließlich von der Mitte, ja sogar von der Gegenseite zu kommen. Obwohl weiter nichts geschieht, als daß man auf das 2. Ohr ein Rauschen gibt, steigt hierbei die Sprachverständlichkeit erheblich an. Sie erreicht ein Maximum, wenn das Geräusch auf dem 2. Ohr um 10 dB lauter ist als auf dem 1. Ohr, das Geräusch + Sprache erhält, nimmt aber bei noch größerer Geräuschlautstärke wieder ab (Abb. 1).

Entscheidend ist allerdings, daß es sich auf beiden Ohren um dasselbe Rauschen handelt, daß es kohärent ist, wie der Fachausdruck heißt. Die

Rauschspannung für den rechten und linken Kopfhörer muß also zur gleichen Zeit aus demselben Rauschgenerator entnommen werden. Es dürfen wohl gewisse Umwandlungen vorgenommen werden, z. B. kann die Rauschspannung auf der einen Seite in der Phase um 180° gedreht werden; das ändert nichts Grundsätzliches an der Korrelation beider Geräusche und es ändert nichts an den psychoakustischen Phänomenen. Nimmt man aber 2 Geräusche, die sich nur statistisch gleichen, die wohl eine gleiche Frequenzzusammensetzung und Amplitudenverteilung haben, aber nicht kohärent sind, dann bleibt der Effekt auf das Sprachverständnis aus.

Jetzt gehen wir von der Endsituation dieses Versuches aus. Sprache wird also nur auf ein Ohr gegeben, kohärentes Rauschen in gleicher Intensität auf beide Ohren, die Sprachverständlichkeit ist gut. Nun mischen wir in allmählich steigender Intensität die Sprache auch dem Geräusch des 2. Ohres bei. Und da geschieht etwas Paradoxes (Abb. 2): in dem Maße, in dem wir die Sprache auf dem 2. Ohr verstärken, nimmt die Verständlichkeit wieder ab. Für den Beobachter stellt sich das subjektiv so dar: er hört die Sprache zunächst von der Seite, das Störgeräusch hat Mitteneindruck. Dann wandert durch Änderung des interauralen Intensitätsverhältnisses die Sprache scheinbar ebenfalls in die Mittellinie und dabei verschlechtert sich die Verständlichkeit.

Wir haben also jetzt folgende Situation: Sprache und Geräusch in gleicher Lautstärke auf beiden Ohren, beide Schallquellen scheinen aus der gleichen Richtung zu kommen, das Sprachverständnis ist schlecht. Jetzt setzen wir den anderen Parameter des binauralen Hörens, nämlich eine interaurale *Laufzeitdifferenz* ein, um beide Schallquellen im subjektiven Wahrnehmungsraum zu trennen. Wir schalten eine elektronische Verzögerungskette in die Zuleitung des Sprachsignales zu dem *einen Ohr* ein und bewirken damit, daß dieses Ohr das Sprachsignal um Bruchteile einer Millisekunde später erhält als das andere Ohr. Die Intensitäten bleiben dabei unverändert.

Subjektiv scheint die Sprachschallquelle dadurch zu der Seite des vorlaufenden Ohres zu wandern, während das Geräusch seinen Mitteneindruck beibehält. Jetzt steigt das Sprachverständnis wieder erheblich an (Abb. 3), und zwar signifikant mehr als bei den Versuchen mit Lautstärkendifferenzen. Umgekehrt kann man natürlich auch dem Geräusch durch Lautzeitdifferenz einen Seiteneindruck geben und der Sprache den Mitteneindruck lassen. Der Effekt auf die Sprachverständlichkeit ist genau der gleiche (Abb. 4).

Was geschieht aber nun, wenn man bei diesen Versuchen inkohärente Geräusche verwendet? Subjektiv nimmt der Beobachter dann 2 verschiedene Geräusche wahr, eines rechts, das andere links. Die Sprache hat dagegen Mitteneindruck, so daß insgesamt 3 Schallquellen räumlich unterschieden werden. Wird jetzt der Sprache durch eine Zeitverzögerung ein Seiteneindruck gegeben, so scheint sie mit dem einen oder dem anderen Geräusch räumlich zusammenzufallen. Überraschenderweise ändert sich hierbei das

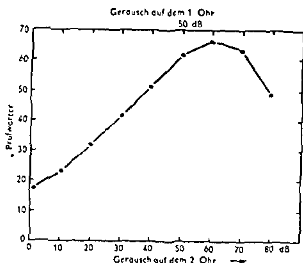


Abb. 1

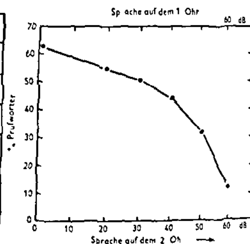


Abb. 2

Abb. 1. Änderung des Sprachverständnisses unter folgenden Versuchsbedingungen: das 1. Ohr erhält Sprache und Geräusch in gleichbleibender Intensität von 50 dB in einem für das Sprachverständnis kritischen Störabstand, sodann wird dasselbe kohärente Geräusch ohne Sprache auf das 2. Ohr in steigender Intensität gegeben. Mittelwerte von 10 Versuchspersonen.

Abb. 2. Änderung des Sprachverständnisses unter folgenden Versuchsbedingungen: Beide Ohren erhalten kohärentes Rauschen von 60 dB Lautstärke. Dem 1. Ohr wird Sprache in gleichbleibender, für das Sprachverständnis kritischer Intensität gegeben, dann wird dem 2. Ohr dieselbe Sprache in steigender Intensität zugeführt, bis derselbe Pegel wie auf dem 1. Ohr erreicht ist. Mittelwerte von 10 Versuchspersonen.

men dieser spezifischen Leistung beteiligt sind. Auf Einzelheiten der Versuchsanordnung kann ich hier leider nicht eingehen, sondern muß mich darauf beschränken, einige der wichtigsten Ergebnisse vorzutragen.

Zunächst haben wir Sprache, d. h. Zahlwörter, über Kopfhörer auf ein Ohr gegeben und gleichzeitig ein weißes Geräusch in einem solchen Intensitätsverhältnis beigemischt, daß nur etwa 20% der Wörter richtig verstanden wurden. Das entspricht also der Situation des Einohrigen, der Sprache bei einem extrem hohen Störpegel zu verstehen sucht. Sodann haben wir dem anderen Ohr dasselbe Geräusch ohne Sprache in steigender Intensität dazugegeben. Die Sprache wird während des ganzen Versuches als von der Seite kommend wahrgenommen. Das Störgeräusch hat zunächst die gleiche scheinbare Einfallsrichtung, verlagert sich aber dann durch Änderung der interauralen Lautstärkenverhältnisse und scheint schließlich von der Mitte, ja sogar von der Gegenseite zu kommen. Obwohl weiter nichts geschieht, als daß man auf das 2. Ohr ein Rauschen gibt, steigt hierbei die Sprachverständlichkeit erheblich an. Sie erreicht ein Maximum, wenn das Geräusch auf dem 2. Ohr um 10 dB lauter ist als auf dem 1. Ohr, das Geräusch + Sprache erhält, nimmt aber bei noch größerer Geräuschlautstärke wieder ab (Abb. 1).

Entscheidend ist allerdings, *daß es sich auf beiden Ohren um dasselbe* Rauschen handelt, daß es kohärent ist, wie der Fachausdruck heißt. Die

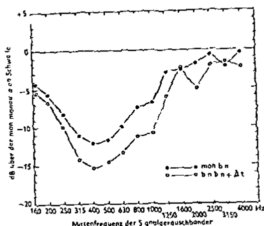


Abb. 5. Änderung der Mithörschwellen von terzbreiten Geräuschbändern in kohärentem Breitbandrauschen bei verschiedenen Bedingungen des binauralen Hörens, bezogen auf den Schwellenwert bei rein monauraler Darbietung mon/bin = Signalgeräuschband nur in einem Ohr, Breitbandgeräusch in seitengleicher Lautstärke auf beiden Ohren bin/bin + Δt = Signalgeräuschband und Breitbandgeräusch auf beiden Ohren in seitengleicher Lautstärke Dem Signalgeräuschband wird durch eine interaurale Laufzeitdifferenz von Δt = 0,648 msec ein maximaler Seiteneindruck gegeben Mittelwerte von 10 Versuchspersonen

beschriebenen Phänomene, und ihre Größenordnung in Dezibel (Abb. 5). Hier sind statt der Sprache die Mithörschwellen von terzbreiten Geräuschbändern in kohärentem Breitbandgeräusch bestimmt worden Bezugswert ist die Mithörschwelle für die rein monaurale Darbietung Die Kurven stellen also den Gewinn des effektiven Störabstandes durch das binaurale Hören dar Man erkennt, daß die Phänomene am stärksten in den Frequenzen um 300–600 Hz ausgeprägt sind und oberhalb 1200 Hz praktisch nicht mehr zum Tragen kommen Durch reine Intensitätsdifferenzen (die Kurve mit den schwarzen Punkten) werden Verbesserungen um durchschnittlich 12,5 dB, bei einzelnen Versuchspersonen bis zu 17 dB erzielt, durch Laufzeitdifferenzen (die Kurve mit den Kreisen) Verbesserungen um durchschnittlich 15,5 dB, bei einzelnen Versuchspersonen bis zu 24 dB

Die praktische Bedeutung dieser Phänomene mag durch folgende Überlegungen unterstrichen werden Normale Sprache hat das Maximum ihrer akustischen Energie in dem Frequenzgebiet um 200–600 Hz, und besonders dann, wenn der Hörer sich seitlich neben oder gar hinter dem Sprecher befindet, wie es ja im täglichen Leben oft vorkommt, stützt sich das Sprachverständnis ganz überwiegend auf diese tiefen Frequenzbereiche, da die höheren vom Mund des Sprechers stärker gebündelt abgestrahlt werden Es erscheint daher sehr sinnvoll, daß die Verbesserung des wirksamen Störabstandes durch die physiologischen Mittel des binauralen Hörens gerade in diesem Frequenzgebiet ansetzt

Eine Verbesserung des Störabstandes um 10 oder 15 dB mag vielleicht

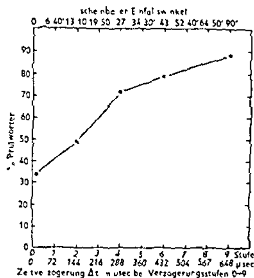


Abb 3

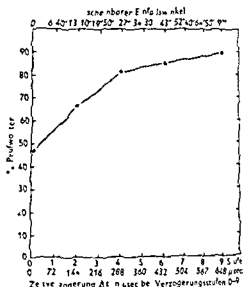


Abb 4

Abb 3 Änderung des Sprachverständnisses unter folgenden Versuchsbedingungen beide Ohren erhalten kohärentes Rauschen und Sprache in gleichbleibender Intensität Sodann wird der Sprache durch eine stufenweise interaurale Zeitverzögerung eine scheinbare Einfallsrichtung von der Seite gegeben Mittelwerte von 10 Versuchspersonen

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Sprachverständnis in keiner Weise, es wird also nicht schlechter, wie vielleicht zu erwarten gewesen wäre

Nach diesen Grundversuchen liegt es naturlich nahe, beide Parameter Intensitätsdifferenz und Laufzeitdifferenz, mit einander zu kombinieren Ich mochte Sie aber nicht mit einer Beschreibung aller denkbaren Kombinationen, die wir untersucht haben, langweilen, sondern nur kurz das Ergebnis skizzieren Die Wirkungen beider Parameter auf die Signalerkennung im Geräusch lassen sich weder summieren noch gegenseitig aufheben, so wie etwa ein durch Laufzeitdifferenz bedingter Richtungseindruck durch eine Intensitätsdifferenz kompensiert werden kann

Die wesentliche Erkenntnis aus diesen Versuchen ist wohl die folgende *Die Verbesserung des effektiven Störabstandes durch das binaurale Hören* ist im Experiment nicht unbedingt an die Tatsache geknupft, daß Signalschallquelle und Störschallquelle subjektiv räumlich getrennt sind Entscheidend scheint zu sein, daß beide Komponenten, das Signal und das Störgeräusch, zwischen beiden Seiten korreliert sind, sich aber auf jeder Seite in ihrer *Zuordnung* zu einander unterscheiden, denn dann konnen sie als *Gestalt* und *Grund* gegen einander abgegrenzt werden, unabhängig davon, ob sie im subjektiven Wahrnehmungsraum unter dem *gleichen* oder *verschiedenen* Einfallswinkeln erscheinen

Abschließend noch ein kurzer Blick auf die Frequenzabhängigkeit der

R Mittermaier Mein Mitarbeiter Roser ist aufgrund seiner Arbeiten über das Richtungshören zu der Überzeugung gekommen daß man bei binauralem Hören einmal eine sogen Fusion d h die Vereinigung zu einer einzigen Hörempfindung und andererseits eine sogen zentrale Synthese annehmen müsse Der erste Vorgang dem der Richtungseindruck zu verdanken ist ist passiv zu verstehen Durch zentrale Synthese dagegen werden besondere Abweichungen zwischen rechts und links zu einer einheitlichen akustischen Wahrnehmung koordiniert z B bei alternierenden Rechts Links Impulsen oder falls dem einen Ohr höherfrequente und dem anderen Ohr tieferfrequente Töne angeboten werden Dieses ist als ein weitgehend aktiver Vorgang zu denken Dazu gehören auch differente Schallbilder mit gemeinsamer Komponente wobei der gemeinsame Anteil durch Fusion binaural die nicht fusionierten Anteile dagegen beiderseits jeweils monaural gehört werden Ähnliches gilt auch von den Intensitätsunterschieden deren gemeinsamer Anteil binaural verarbeitet deren überschüssige Intensität jedoch monaural wahrgenommen wird Ich möchte Herrn Feldmann fragen ob seine Untersuchungen nicht die von Roser aufgestellte Hypothese bestätigen

H Feldmann (Antwort) Die von Prof *Huizinga* erwähnte Cocktailparty Situation war der eigentliche Ausgangspunkt unserer Untersuchungen Der Zweiohrige hört ja das allgemeine Geräusch der Party mit beiden Ohren praktisch gleich laut Er wendet sein eines Ohr dem Sprecher zu und erreicht dadurch daß das erwünschte Sprachsignal mit einer großen interauralen Lautstärkendifferenz aufgenommen wird Der Versuch 1 den ich schilderte ahmt genau diese Situation nach Das Geräusch auf dem zweiten Ohr ist aber wichtig für das Sprachverständnis denn nur mit Hilfe des Vergleiches zwischen beiden Seiten kann das Sprachsignal durch zentralnervöse Mechanismen aus dem Geräusch isoliert werden Man kann sich als Modell vorstellen daß die Eingänge beider Ohren voneinander subtrahiert werden Dann hebt sich das Geräusch auf und das Sprachsignal tritt klar hervor Der Einohrige ist deswegen schlechter gestellt weil ihm diese Vergleichsmöglichkeit der Erregungsmuster beider Ohren fehlt

M Mittermaier Möchte ich sagen daß wir zunächst die Vorstellung hatten daß diese Phänomene des binauralen Hörens unmittelbar mit dem Richtungsgehör verknüpft sind Wir haben aber wie ich ausführte experimentell Situationen erzeugen können die in der normalen akustischen Umwelt nicht vorkommen in denen Signalschall und Störschall unter dem gleichen Einfallswinkel erscheinen und dennoch wird der Störabstand durch das binaurale Hören stark angehoben Wir möchten daraus schließen daß die zugrundeliegenden zentralnervösen Mechanismen für das Richtungsgehör und die beschriebenen psychoakustischen Phänomene nicht identisch sind Aber die Fusion spielt sicher für beide eine überragende Rolle

auf den ersten Blick nicht sehr erheblich erscheinen Man muß aber bedenken, daß 10 dB einer Änderung der Hörweite etwa um den Faktor 4 entsprechen d h wenn ein Zweiohriger in einer bestimmten Situation unter Störgeräuschen Sprache noch auf 4 m versteht, dann wird der Einohrige sie nur auf 1 m Entfernung verstehen und damit ist er doch ganz wesentlich schlechter gestellt abgesehen davon daß er auch das Richtungsgehör weitgehend verloren hat

Diese interessanten Phänomene des binauralen Hörens regen natürlich zu mannigfachen Deutungsversuchen an, aber darauf kann hier nicht mehr eingegangen werden Wichtiger ist es vielleicht die Erkenntnis mit in die ärztliche Praxis hinüberzunehmen daß die zwei Ohren ein Organsystem bilden dessen Leistungen weit über die des Einzelorganes hinausgehen

SUMMARY

Psychoacoustic experiments of the author have shown that the effective signal to noise ratio is considerably raised by binaural hearing if certain parameters (intensity time delay) of both components differ in both ears The effect of these factors is examined (influence of frequency coherence etc) and the results are discussed in view of the central nervous mechanisms evaluating binaural information

RÉSUMÉ

Des expériments psychoacoustiques de l'auteur ont démontré qu'en audition binaurale le seuil effectif du signal sous l'influence du bruit est amélioré considérablement lorsque certains facteurs (intensité phase) ne sont pas les mêmes pour les deux oreilles L'effet de ces facteurs est examiné (l'influence de fréquence de cohérence etc) et les résultats sont discutés en considération de l'élaboration de l'information binaurale par le système nerveux central

LITERATUR

FELDMANN H 1963 Untersuchungen über das binaurale Hören unter Einwirkung von Störgeräuschen *Arch Ohr Nas Kehlkopfheilk* 181 337 374

Univ Hals Nasen Ohren Klinik
(9 Heidelberg) Voßstr Westdeutschland

DISCUSSION

L Huizinga Hat mit sehr viel Interesse den Vortrag von Kollege Feldmann gehört Er hat die Cocktailparties besprochen Diese sind nicht nur wissenschaftlich aber auch sozial wichtig Wir armen Europäer müssen versuchen hier auszukommen Nun gibt es einen Trick es wundert mich daß Dr Feldmann nicht darüber gesprochen hat Man muß das eine Ohr gegen den Partner wenden und das andere Ohr gegen den background noise Ist es so kein Vorteil wenn das andere Ohr vollkommen taub ist?

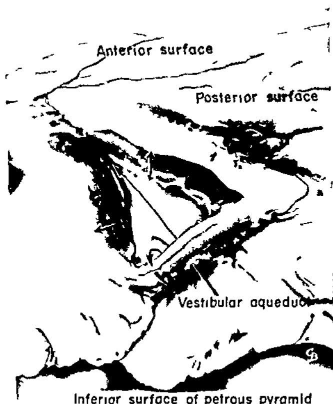


FIG 1 Drawing of a specimen of right temporal bone medial surface Demonstrating the form and position of the external aperture of the vestibular aqueduct and the distal intraosseous portion of the latter The overlying bone has been removed to the depth indicated by the small arrows a bridge of bone (encircled) remains to record topographically the position of the aperture An elongate arrow marks the former course of the endolymphatic sac into the narrow segment of the aqueduct

carried beyond it by transudation, some less refined histological structures must care for its ultimate reclamation by the blood vascular system

For each of the aqueducts the order of presentation will be as follows gross anatomy development, adult histology In closing, the similarities and differences between the two channels will be reviewed

MATERIAL AND METHODS

The structural features are herein demonstrated by drawings of dissected temporal bones and by photomicrographs of transverse series in the otological collection at the University of Wisconsin, prepared with the supervision of the late Theodore H Bast *

* Drawings by George Buckley photomicrographs by Homer Montague labelling of the prints by Jane Gordon The photomicrographs were taken from the following series in the Wisconsin Collection Figure 2 series 159 3, series 131 [illegible] series 105 7a and 7b series 21 8a to 8c 124 9 series 83

THE ENDOLYMPHATIC AND PERILYMPHATIC AQUEDUCTS OF THE HUMAN EAR

Developmental and Adult Anatomy of their Parietes and Contents in Relation to Otological Surgery[1]

BARRY J. ANSON
Iowa City, Iowa, U S A

From the Department of Otolaryngology and Maxillofacial Surgery, College of Medicine, State University of Iowa

The fetal development of both the vestibular and cochlear aqueducts will be followed in otological series beginning with the 4 month stage Postnatal progress and mature structure will be traced from the new-born infant to the adult of 70 years (in dissections, serial sections and reconstructions prepared from the latter)

These features will be emphasized histology of the osseous wall and the contained connective tissue, source and course of blood vessels *derived from labyrinthine periotic tissue internally and meningeal layers* externally, normal range in adult anatomy On these structural bases, *the two channels will be compared, with special reference to their* present and prospective role in otological surgery

INTRODUCTION

It is the purpose of the present paper to discuss the anatomy of the cochlear and vestibular aqueducts in man as intermediaries between perilymph and cerebro-spinal fluid In the light of recent surgery on the cochlear canaliculus in man, the mechanism calls for critical appraisal The pioneering work of Dr William House, followed by the trilogy of reports by Dr House, Dr Portmann and Dr Allen, lends a degree of urgency to morphological study [2]

Obviously, no matter how intricately fabricated may be the cytological mechanism by which fluid is produced in the epithelial duct-system and

[1] Guest lecture at the 1964 Wurzburg meeting of the Collegium Oto Rhino Laryngologicum Amicitiae sacrum Paper read by George E Shambaugh Jr M D in the author s unavoidable absence The writer wishes to thank the Committee for its graciousness in this matter and Dr Shambaugh for his generous aid

A study conducted with the support of the Central Bureau of Research of the American Otological Society and the National Institutes of Health of the U S Public Health Service (grant no NB 03855 02)

[2] Otosclerosis Little Brown and Company, Boston 1962 *A M A Archives of Otolaryngology* vol 79 1964 pages 338 354 328–337, 322 327

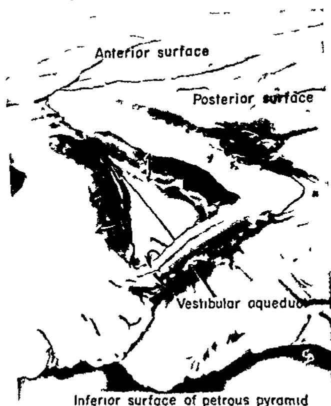


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[2] Drawings by George Buckley, photomicrographs by Homer Montague, labelling of the prints by Jane Gordon The photomicrographs were taken from the following series in the Wisconsin Collection Figure 2, series 158, 3 series 131, 6 series 105, 7 a and 7 b series 21, 8 a to 8 c 121, 9 series 85

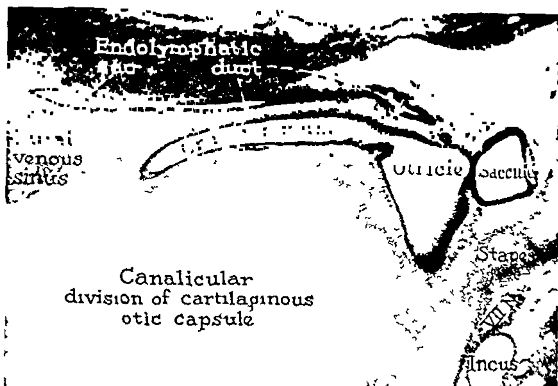


Fig. 2. Photomicrograph showing the early stage in the development of the otic capsule in the region of the vestibular aqueduct. The endolymphatic duct is already partially enclosed by the cartilaginous wall of the vestibular aqueduct. Fetus of 8 1/2 weeks (28 mm crown rump length). ×50

OBSERVATIONS AND DISCUSSION

Vestibular Aqueduct and Endolymphatic Duct

Variations in form, position and size of the vestibular aqueduct are frequent. However, in almost every instance the aperture opens upon the posterior surface of the petrous pyramid. The aperture is regularly elongate and oblique (Fig. 1).

When the interior of the vestibular aqueduct has been exposed by removal of the overlying bone it becomes clear that the space at this distal extremity is far greater than would be required to accommodate the endolymphatic sac. The saccus, in fact, occupies only a fraction of the funnel-shaped space. The remainder contains a connective tissue continuous with the cranial *dura mater*. This tissue assumes an areolar character around the *saccus*, thereby resembling the arachnoid tissue of the cochlear canaliculus (or aqueduct). It is vascular, the vessels communicate with those in the wall of the aqueduct (hereinafter).

The fundamental difference between the vestibular and cochlear aqueducts is established as soon as the endolymphatic appendage of the primitive otocyst becomes surrounded by the precartilage of the embryonic otic capsule.

At the stage marking the passage from the embryonic to the fetal condi-

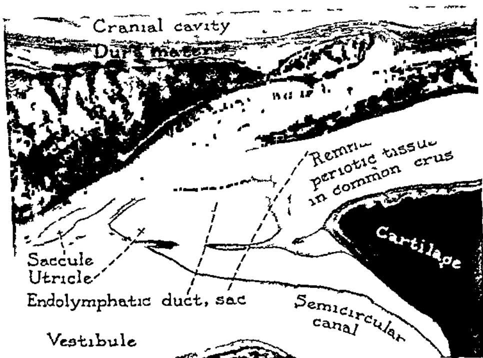


FIG 3 Photomicrograph presenting an intermediate stage in the formation of the capsule The wall of the vestibular aqueduct is undergoing ossification The *saccus* prolonged beyond the aperture of the aqueduct occupies a fovea on the posterior surface of the developing petrous pyramid Fetus 20 weeks (1 0 mm) ×22

tion the basic form and relationships are already evidenced In the specimen of 2 months the proximal part of the wall of the vestibular aqueduct is formed in cartilage (Fig 2) The endolymphatic appendage is widening at the distal end forecasting the definitive subdivisions Peripheral to these portions of the epithelial duct system precartilage is undergoing resolution predicting the production of a vacuolated fibrous network whose progressively widening interspaces will become the perilymphatic labyrinth (Fig 3) The *saccus* is already imbedded in meningeal tissue near the dural venous sinus (Fig 2)

In the 4 month fetus ossification centers appear in the wall of the aqueduct In a fetus one month older, bone completely encloses the aqueduct (Fig 3) In the newborn infant ossification is complete

Textbooks heretofore have regularly failed to consider the interfibrillar spaces of the tissue around the endolymphatic duct and sac as constituting a route of movement for the perilymph[4] These spaces would seem to be important because as the external aperture of the aqueduct is approached

[4] Herein rests a controversy, a review of which is beyond the scope of a paper read at a meeting Some noteworthy opinions have already been presented in an earlier article (The Laryngoscope 1964, vol 74, pp 945–966)

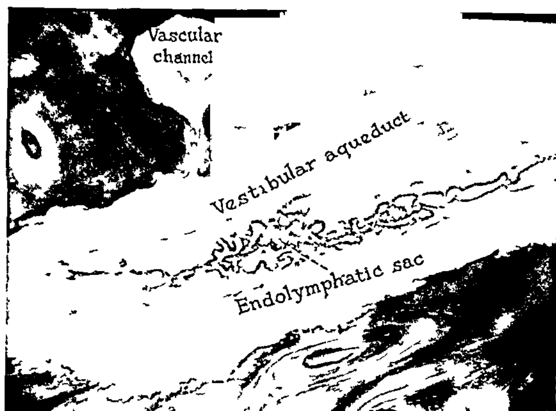


Fig. 4. Photomicrograph of the *saccus endolymphaticus* near its distal extremity and the vestibular aqueduct [illegible] connective tissue the sac is lodged. Blood vessels [illegible] the surrounding bone send branches into the aqueduct to reach the loosely textured tissue that immediately surrounds the duct and sac. Adult, [illegible] years of age. × 80

it is occupied by a process of the cranial *dura mater*. Blood vessels enter and leave the aqueduct; they are continuous with those in the connective tissue that immediately surrounds the sac (Fig. 4). It is suggested that their capillary extensions may assist in resorptive capacity for the labyrinthine fluids.

The pattern of the intradural vessels is evident in many cleaned specimens of temporal bone: their lesser sulci are continuous from the external aperture of the aqueduct to the more capacious sigmoid and petrosal sulci and even to such openings as the internal acoustic meatus and the subarcuate fossa.

The vestibular aqueduct is thus provided with an internal venous mechanism which, as will be shown, is wholly wanting in the case of the cochlear aqueduct.

Cochlear Aqueduct and Perilymphatic Duct

The cochlear aqueduct and its so called perilymphatic duct will now be compared with the vestibular aqueduct and the contained endolymphatic sac.

It is to be recognized initially that when divested of soft tissues the coch

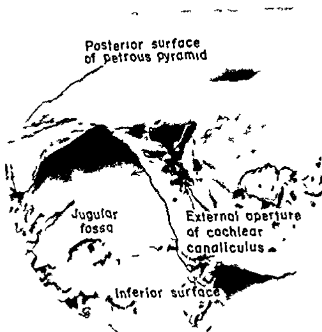


Fig. [illegible]. Drawing of a specimen of a left temporal bone, inferomedial aspect. Demonstrating the form and relations of the external aperture of the cochlear aqueduct (or canaliculus). The unlabelled arrow traverses a communication between the funnel-shaped aperture and the jugular fossa.

lear aqueduct resembles the vestibular (Fig. [illegible]). Here relationships are of primary importance. On this inferior surface of the pyramid are situated the jugular fossa (for the bulb of the superior jugular vein). Just medianward from the jugular fossa opens a triangular, funnel-shaped depression in the depths of which is seen the external aperture of the cochlear canaliculus for the so-called *vena canaliculi cochleae* and *ductus perilymphaticus*. Situated in front of the jugular fossa is the large round opening, the *foramen caroticum externum*, that forms the entrance of the *carotid canal* (for the internal carotid artery, the internal carotid venous plexus, and the corresponding plexus of nerves derived from the cephalic and cervical parts of the sympathetic system).

As will be shown, the *vein occupies* a separate channel, and the content of the cochlear canaliculus could qualify for designation as a duct only in the sense of possessing a fabric permeable to fluid.

In the latter connection it is important to record that once the vein of the cochlear canaliculus reaches *meningeal level* the possibilities for venous communication with larger vessels match those obtaining in the case of the vestibular aqueduct.

The above-described features are established early in the course of development. They will now be briefly reviewed.

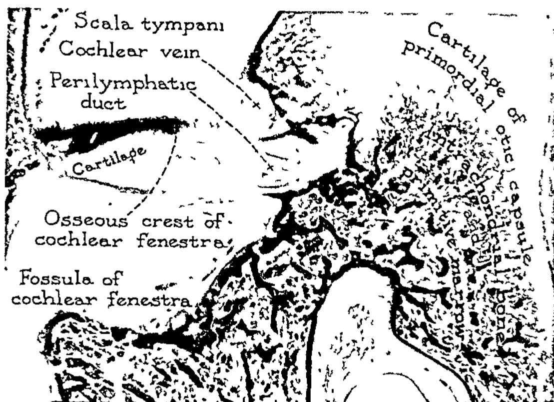


Fig 6 Photomicrograph showing an early stage in the development of the cochlear aqueduct and the perilymphatic duct At this internal aspect of the aqueduct the channel for the cochlear vein is being separated from the so called perilymphatic duct Fetus of 20 weeks (167 mm) × 22

In a 4-month fetus the perilymphatic duct makes its appearance immediately internal to the rim, or crest, of the cochlear (round) window The cartilage rim undergoes resolution, the process matching that by which the perilymphatic spaces are formed, at an earlier stage, around the membranous duct-system *As a result of this process, the aqueduct (or canaliculus)*, containing the "duct", becomes a channel through the otic capsule, the duct itself is nothing more than connective tissue within the newly-formed aqueduct Unlike the vestibular aqueduct, the formation of the cochlear canaliculus is, therefore, secondary Four developmental steps will be illustrated

In the developing otic capsule of the 5-month fetus, bone-formation is taking place in the wall of the aqueduct (Fig 6) The vein is already partly separated from the duct

In the 6-month fetus both the perilymphatic duct and the cochlear vein are enclosed in complete and independent bony channels The tissue within the aqueduct is not vascular (Figs 7 *a* and 7 *b*)

At birth, the perilymphatic channel has attained mature form and histological fabric (Figs 8 *a* to 8 *c*) At the internal aperture, the contained tissue becomes continuous with the periotic lining of the *scala tympani* (Fig 8 *a*) In midcourse the content is similar (Fig 8 *b*) At the external

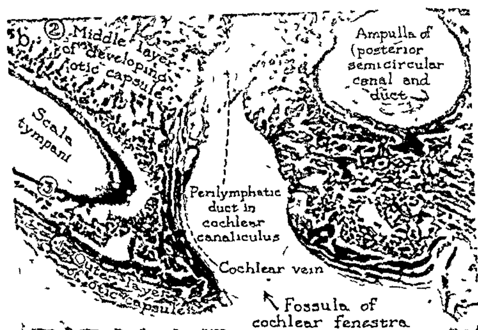


Fig. [illegible] Photomicrographs showing an intermediate stage in the formation of the cochlear aqueduct and the channel for the cochlear vein (*a*) at the transverse level of the internal aperture of the aqueduct (*b*) in intra-osseous course. The constituent layers of capsule are numbered in both *a* and *b*. In *a* the margins of the *crista* of the cochlear *fenestra* are indicated by unlabelled arrows and a remnant of primordial cartilage is marked by
Fetus of 21 weeks, 183 mm. *a* × 17, *b* × 15.

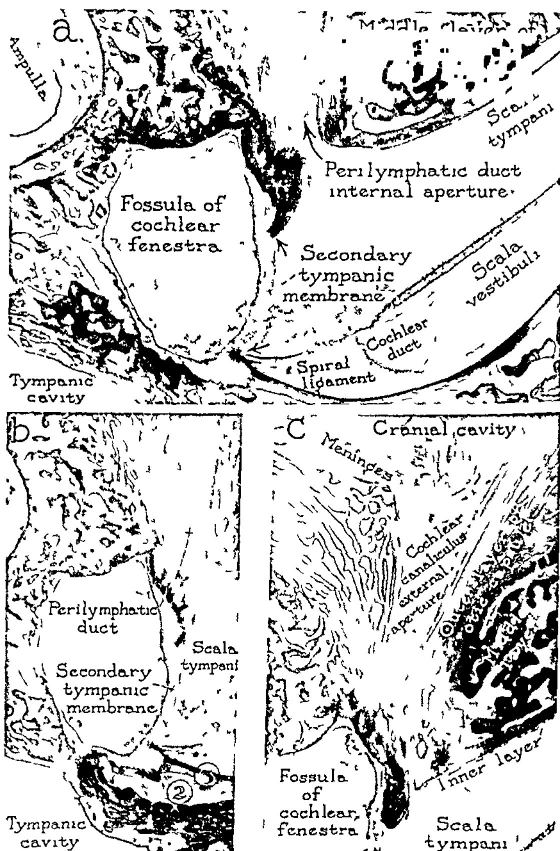


Fig. 8.—Photomicrographs demonstrating the maturing form of the cochlear aqueduct and of the contained perilymphatic duct: *a*, at the internal aperture of the aqueduct; *b*, its intraosseous course; *c*, at the external aperture (with a remnant of the *dura mater encephali*). Newborn infant (4 days premature). ×21.

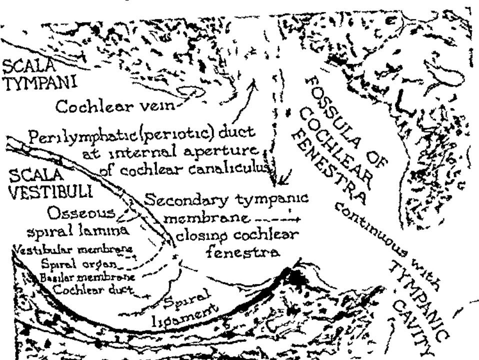


Fig. 9.11 Tomicrograph of the cochlear aqueduct and the channel for the vein together with the related structures at the level of continuity of the so-called *duct with the scala tympani*. The unlabelled arrows point to the *crista* of the *fenestra cochleae*. Infant of [illegible] weeks ×2[illegible]

aperture (in the same specimen) the tissue merges with the periosteal layer of the cranial meninges (Fig. 8c). In the infant as in all more advanced stages the vein remains independent (Fig. 9).

The ordinary character of the fabric is evident. It contains no duct; it transmits neither vein nor artery. The cerebrospinal fluid would be obliged to pass through the interfibrillar tissue spaces in cases of otorrhea.

Capacity is an important feature in the flow of any fluid. In 10 dissected temporal bones from adult specimens the average diameter of the internal aperture of the cochlear aqueduct was 0.09 mm with a range of 0.05 to 0.125 mm. The average dimension for the external aperture was 0.83, the range being 0.5 to 1.25 mm. These measurements were made 1 to 2 mm inside of the funnel-shaped widening where the aqueduct opens upon the surface of the bone (at which depth the true aqueduct may be regarded as beginning). The average length is 11.5 mm (range 10.0 mm to 14.0 mm).

The internal aperture of the vestibular aqueduct is considerably larger than the corresponding opening of the cochlear channel. The average diameter was 0.35 mm (range 0.25 to 0.5 mm). The external aperture of the aqueduct is a flattened fissure rather than a circular pore. Its average width was 3.2 mm (range 0.85 to 4.75 mm). The height decreases from the

anteromedial end to the posterolateral, where the walls meet at a pı The average height at the former extremity was 0 52 mm (range, 0 2 0,7 mm). The average length is 7.1 mm (range, 3 5 mm to 12 0 mm).

SUMMARY

By way of summary, the two aqueducts may be compared (Fig 10) cochlear aqueduct (or canaliculus) contrary to conventional descriptions, tı *mits neither a vein nor an artery; from an early fetal stage, onward through* the related vein is housed in a separate osseous channel The vestibular aque unlike the cochlear, contains both arteries and veins that enter the connec tissue *from canals in the surrounding bone and from the cranial meninges*

Both aqueducts are occupied by connective tissue, which is as loosely text around the endolymphatic sac as is the entire fibrous content of the coch aqueduct, the interstices of which constitute the so-called *perilymphatic* "dı The tissue within the two aqueducts resembles that through which fluid ge ally moves in other parts of the body.

Two additional features are similar: the aqueducts, cochlear and vestibı open internally upon the wall of the osseous labyrinth (containing the p lymph); both terminate externally in orifices situated on surfaces of the petı pyramid This means that both channels begin in periotic tissue and termı in the meninges.

The chief differences are two in number · the wall of the vestibular aque is formed around a pre-existent duct and sacculation of the membranous l rinth, whereas the cochlear aqueduct is of secondary formation, produced thro the resorption of precartilage of the developing otic capsule of the fetal ear, vestibular aqueduct contains the endolymphatic duct and sac together w related arteries and veins, whereas the cochlear aqueduct contains none of th (the cochlear vein occupying a separate osseous channel, adjacent to the ac duct).

Therefore, on structural grounds, it seems probable *that both aqueducts* i participate in the function of maintaining a stage of balance in the fluid sys of the internal ear At least, the morphological similarities lead to such a con *sion, differences seem to be in the category of degree, not that of kind*

Admittedly, much remains to be learned about the mechanism of physiolog exchange between the labyrinthine and the cerebrospinal fluids For furt structural study the primary need is for specimens which preserve the less "d able" meningeal layers, that is, *arachnoidea* and *pia mater* Currently avail histological material includes only that segment of the entire pathway wh ends on the external aperture in the cranial *dura mater*

The latter study, now in progress, will include a re-examination of the vascu channels in and around both aqueducts This aspect of otological anatomy l been chronically neglected

It is conceivable that present concepts of *function are dependent to an* ordinate degree, upon a terminology which fallaciously suggests a single functı for each aqueduct to the exclusion of a second service in the case of t vestibular aqueduct, the latter may be part of the perilymphatic as well as t endolymphatic labyrinthic system

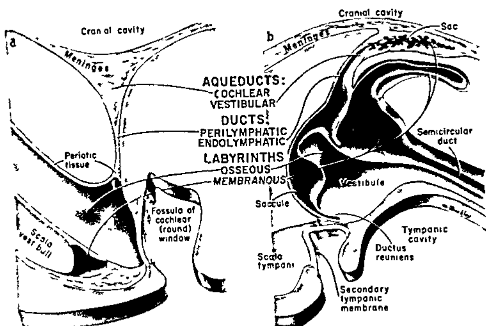


Fig. 10 Cochlear and vestibular aqueducts perilymphatic and endolymphatic ducts Semischematic Comparative labelling *(reproduced with permission of The Laryngoscope)*

RESUME

Le développement fœtal de l'aqueduc du vestibule et celui du limaçon est présenté a l'aide de séries otiques commencant avec un fœtus de quatre mois On poursuit le progrès postnatal et la structure dans l'homme adulte a partir du nouveau ne jusqu'a d'age de 70 ans à l'aide des preparations de coupes micro scopiques et des reconstructions

Les aspects suivants seront mis en relief l'histologie de la paroi osseuse et le tissu conjonctif l'origine et le cours des vaisseaux sanguins derives du tissu pe riotique (osseus) du limaçon à l'interieur et ceux des meninges a l'exterieur, les variations normales chez l'homme adulte Les deux canaux sont compares en relation à leur role présent et future dans la chirurgie otique

ZUSAMMENFASSUNG

Die embryologische Entwicklung des Aquaeductus vestibuli und des Aquae ductus cochleae wird anhand menschlichen Materials in Serien (bei einem vier-*monatigen Fotus* begonnen) untersucht Die Entwicklung nach der Geburt wird vom Neugeborenen bis zum siebzigjahrigen Erwachsenen anhand von Praparaten, Serienschnitten und Rekonstruktionen verfolgt

Besonders berucksichtigt werden folgende Gesichtspunkte die Histologie der knochernen Wande das darin enthaltene Bindegewebe, der Ursprung und Verlauf von Blutgefassen welche im knöchernen Gewebe des Labyrinthes *von innen* her und in den Hirnhautschichten von aussen her ihren Ursprung nehmen, ihre normalen Variationen beim Erwachsenen Die beiden Kanale werden aufgrund ihres Baues miteinander verglichen wobei besonders ihre *Rolle* in der heutigen sowie in der zukunftigen Chirurgie des Ohres berucksichtigt wird

Dept of Otolaryngology College of Medicine
State University of Iowa Iowa City Iowa
U S A

DISCUSSION

F Escher Uber das Problem des Abschlusses des Ductus cochlearis gegen die Schnecke wurden in unserer Klinik durch Dr M Neiger folgende Beobachtungen gemacht Beim Rhesusaffen findet sich an der tympanalen Öffnung des Aquae ductus cochleae eine Membran die diesen vollständig vom untersten Schnecken gang abschliesst Es handelt sich um eine cellulare Membran im histologischen Schnitt sind Zellkerne sichtbar Ihre Dicke beträgt ein, hochstens zwei Zellen Sie bildet die Fortsetzung der innersten Schicht des den Schneckengang aus kleidenden Endostes Elektronenoptische Untersuchungen sind im Gang Dieselbe Membran wurde von Waltner beim Menschen auch beschrieben als Membrana limitans oder Barrier Membran

L Sitrala In a study published 1941 I have shown the close connection be tween the epithelial cells of the ductus and saccus endolymphaticus and the bl d vessels in the loose connective tissue in the bony canal of the aqueduct This finding seems to confirm the theory of the resorptive function of endolym phatic duct and sac



Figs 1 and 2 In the epithelial cells of the endolymphatic duct lying in the aquaeductus vestibuli are seen plasma processes (×) extending into the surrounding relatively loose connective tissue and projecting towards the capillaries (× ×)

T J Cawthorne We are grateful to Dr Shambaugh for his clear and elegant presentation of Dr Anson's paper on the cochlear and vestibular aqueducts This paper is very timely in view of the re-awakening of interest in operations on the saccus endolymphaticus originally described by Dr Portmann in 1928 and recently revived in a modified form by Dr William House of Los Angeles

Dr Anson's paper raises my hope that Dr Stacy Guild's view of the formation circulation and reabsorption of endolymph will be given further consideration

Although I have played a small part in the development of destructive operations of the labyrinth in patients with intractable Menière's disease it is my hope that drainage of the endolymphatic sac will eventually prove to be the operation of choice in Menière's disease

G E Shambaugh (Reply) *The observation of Prof Fischer of a thin membrane* closing the external cranial opening of the vestibular aqueduct will be of great interest to Professor Anson His specimens lacked preservation of the dura and pia arachnoid so that he did not observe this membrane Prof *Surala's* earlier demonstration of connections between the cells of the walls of the endolymphatic sac and the vessels of the surrounding connective tissue confirms the view of Anson regarding the resorptive function of these structures

I was particularly interested by Dr *Cawthorne's* views that endolymphatic hydrops is due to increased production or decreased resorption of endolymph I should like at this time to make a suggestion regarding the benefits of William House's and Georges Portmann's operations Dr House very kindly allowed me to study the clinical records of his first 50 shunt operations Two observations impressed me in every *revision the tube introduced from the sac to the cerebrospinal* space was found to be occluded by ingrowth of arachnoid connective

tissue In every patient on whom a shunt was carried out there was an initial rather marked drop in hearing both by air and by bone My suggestion is that after *every* shunt operation the tube becomes occluded, and as it closes the hearing recovers from the initial drop The benefits of the operation may be due to improved blood supply to the sac produced by surgical intervention rather than by connecting the saccus to the cerebrospinal space This suggestion of course *requires* proof by comparing results of simply surgically exposing the sac so as to improve its blood supply, and in addition inserting a shunt tube I predict the benefits will be similar the only difference being that when a shunt tube is introduced there is a worsening of hearing that recovers only when this abnormal situation corrects itself by closure of the tube

THE PATHOLOGICAL TYPES OF COCHLEO-SACCULAR DEGENERATION[1]

Harold F. Schuknecht,[2] Makoto Igarashi[3] and Richard R. Gacek[4]

A pathological study of the specimens in our temporal bone library indicates that there are three conditions in which cochleo-saccular degeneration is found: (1) genetically inherited anomaly; (2) viral diseases, and, (3) aging. A number of mammals present inherited forms of labyrinthine agenesis or degeneration. These include various mutant strains of mice, waltzing guinea pigs, albino cats, and Dalmatian dogs. Cochleo-saccular atrophy is a common pathological finding in deafness due to maternal rubella, postnatally acquired measles, mumps, and sudden deafness. Involvement of the saccule as well as the cochlea as an atrophic process in aging has not been reported previously. Specimens from an aged cat, dog, and human suffering from slowly progressive deafness show atrophic changes in the cochlea and saccule with normal utricle and semicircular canals. In demonstrating a greater susceptibility to injury, the pars inferior (cochlea and saccule) abides by the biological rule that the phylogenetically newer systems in an organism exhibit a greater susceptibility to abuse than do older systems. It seems likely that the cochlea and saccule share a common denominator, phylogenetically determined, which may be metabolic, cytochemical, enzymatic, or possibly microanatomical, and which makes them jointly susceptible to certain genetic alterations, viral diseases, and aging.

Developmental or degenerative changes selectively involving only the *cochlea and the saccule while sparing the remaining* endorgans of the labyrinth were first described by Scheibe (1, 2) in a type of hereditary nerve deafness. This peculiar form of hereditary inner ear defect was confirmed by Marx (3) and others. In animals, a similar type of inner ear change has been known to occur in Dalmatian dogs (4, 5, 6), albino cats (7), waltzing guinea pigs (8, 9), and mice (10).

Only in recent years have reports of cochleo-saccular degeneration in various other otopathological syndromes appeared in the literature. These

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have included prenatally acquired diseases (e g rubella erythroblastosis (11, 12, 13)), and postnatally acquired diseases (mumps, measles, sudden deafness, etc (14, 15, 16 17, 18)) Of particular interest is the fact that the pathological changes have involved selectively the phylogenetically younger part of the labyrinth—the pars inferior

Recently we found cochleo saccular degeneration in the temporal bone specimens of Dalmatian dogs, an aged cat, dog, human and a human suffering from unilateral sudden deafness The purpose of this report is to describe the pathology in these ears as determined by light microscopic sections of serial sections of temporal bones

Types of Cochleo-Saccular Degeneration

Our pathological studies suggest that there are three conditions in which cochleo saccular degeneration is found (1) genetically inherited anomaly, (2) viral diseases, and (3) aging

(1) *Genetically inherited anomaly*

A number of mammals present inherited forms of labyrinthine dysgenesis or degeneration These include various mutant strains of mice, waltzing guinea pigs albino cats and Dalmatian dogs

As an example of this type of hereditary cochleo saccular dysgenesis, we shall describe the findings in the deaf Dalmatian dog (see Fig 1)

Reissner's membrane is depressed and in some areas adherent to the limbus organ of Corti, and spiral ligament The stria vascularis is atrophied throughout The cytological structure of the organ of Corti is flattened and disorganized The pillars are recognizable but are flattened and in some areas overlap the limbus There is poor differentiation of cell types but, in some regions it is possible to recognize distorted Deiter's cells and an occasional hair cell The presence of normal cochlear neurones axons and dendrites in the presence of severe structural alterations of the organ of Corti indicates that the changes occurred during embryological development, for it is well known that acquired pathological alterations of the supporting cells occurring after full development of the organ of Corti results in secondary neuronal degeneration within two to three weeks

The wall of the saccule is collapsed and adherent to a distorted otolithic membrane The supporting cells of the saccular macula appear normal by light microscopy but about half the hair cells are missing The saccular nerve appears normal

The utricle and semicircular canals are normal

(2) *Viral labyrinthitis*

Maternal rubella occurring during the first trimester is a well known cause for bilateral deafness The severity of the hearing loss varies from

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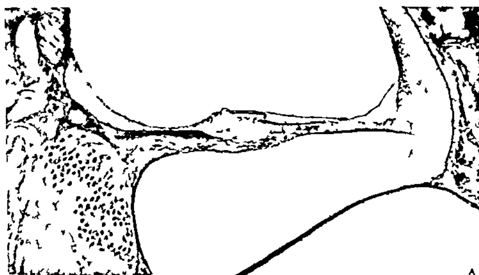
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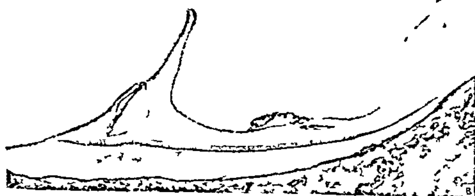
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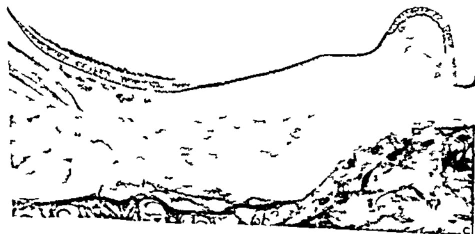
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A


B


C

moderate (with the greatest loss for high frequencies) to total deafness. There are often associated cardiac, brain, and eye alterations. The reason for the peculiar susceptibility of the young embryo to the rubella virus is not known. The pathology as described by Lindsay *et al.* and Altmann (19) consists of atrophic changes in the organ of Corti and saccule with varying degrees of secondary degeneration of the cochlear neurones. The utricle and semicircular canals are normal.

Mumps and morbilli infections in the young child are well known causes for deafness which is usually, but not always, unilateral. The pathological changes have been described by Lindsay *et al.* and are similar to those occurring in maternal rubella.

The reason for bilateral involvement in maternal prenatal rubella and unilateral involvement in postnatal mumps and measles permits some interesting speculations. Possibly the route of infection is different, for example, the virus may reach the inner ear via the blood stream in maternal rubella but more often via the cerebrospinal fluid-perilymph communication in mumps and rubella. It would be of interest to know if a large cochlear aqueduct predisposes to the development of viral labyrinthitis.

In the past, sudden unilateral or bilateral deafness in an apparently healthy individual often has been thought to be of vascular etiology. Recent pathological studies have shown, however, that at least some of these are the result of viral labyrinthitis (18, 21). Probably the best evidence comes from such a case in which histological studies reveal cochleo-saccular degeneration.

Mrs. A. P. In 1933, at the age of 39, this female patient suddenly lost the hearing in her right ear, following a head cold. She had no dizziness during or following the onset of deafness. About the same time she noted a buzzing in the ear which persisted until the time of her death.

An audiometric test performed 14 years later and three weeks prior to death demonstrated a right sensorineural deafness ranging from 40 db for the low frequencies to 70 db for the high frequencies. Loudness recruitment as tested by the binaural loudness balance method was present at 1000 cps. Hearing was normal in the left ear. Caloric tests were not performed.

She died in 1953 at the age of 59 of adenocarcinoma of the colon. About 45 minutes after death 20% formalin solution was injected into both middle ears. The temporal bones were removed at autopsy ten hours later.

Histological examination shows cochleo-saccular degeneration in the right ear (Fig. 2). The organ of Corti is shrunken, the hair cell nuclei are poorly defined,

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Fig. 1. These three photomicrographs show the significant pathological changes in the ear of a deaf Dalmatian dog. (A) The organ of Corti is flattened and disorganized. The tectorial membrane and stria vascularis are atrophied. Reissner's membrane is attached to the organ of Corti to partially obliterate the cochlear duct. The cochlear neurones appear normal. (B) The wall of the saccule is collapsed and folded upon itself. The supporting cells of the saccular macula appear normal and about half of the hair cells are missing. (C) The utricle and cristae are normal.

and the tectorial membrane is atrophied. Reissner's membrane is depressed and adherent to the stria vascularis and to the organ of Corti in some areas. The macula of the right saccule is totally devoid of hair cells, although supporting cells are present. The saccular wall is collapsed and adherent to the underlying shrunken otolithic membrane. The utricular macula and crista are normal.

The left ear appears normal.

(3) *Aging (Presbycusis)*

We have found cochleo-saccular degeneration in an aged cat, dog, and human. Saccular degeneration, as a function of aging, has not been reported previously.

(a) Old cat. A woman brought her aged cat to the laboratory stating that she had personally cared for the animal from the time of its birth—*a period of nineteen years*—and that the animal had suffered from progressive hearing loss for several years. The animal was given pentobarbital sodium intraperitoneally in a dose sufficient to produce deep general anesthesia and was intravitally perfused with Heidenhain-Susa solution.

There is total loss of the organ of Corti in the basal 15 *mm of the cochlea and* in the remaining 8 mm there is an organ of Corti with about 20% of the hair cells remaining (Fig. 3). There is total loss of neurones in the basal 17 mm, partial loss to 21.5, and normal in the remainder of the cochlea. The loss of cochlear neurones is proportional to the changes in the supporting cells indicating it is *of secondary nature*. The stria vascularis is *almost totally missing*. Reissner's membrane is severely atrophic and missing in some regions. The spiral ligament, limbus, and tectorial membrane are normal throughout. The efferent fibers in their intraganglionic course are clearly visible in the basal turn where afferent fibers are totally missing.

There is a loss of about half of the hair cells and *supporting cells in the macula* sacculi (Fig. 4). The otolithic membrane, saccular wall, and saccular nerve appear normal. The macula utriculi and crista *appear normal*.

The findings are nearly identical in the right and left ears.

(b) Old dog. A man brought an aged Dachshund to the laboratory *stating that* the animal was 20 years of age and had suffered progressive loss of hearing for several years and now was totally deaf as well as blind, a statement which appeared to be confirmed by the animal's behavior. The animal was given sodium pentobarbital intraperitoneally to induce deep anesthesia and was intravitally perfused with Heidenhain-Susa solution.

The loss *of hair cells* and changes in supporting cells in the organ of Corti are similar to those *of the cat*, although somewhat less severe (Fig. 5). The loss of cochlear neurones is *proportional to the* extent of atrophy of supporting elements of the organ of Corti *and may* be considered to be of a secondary *nature*. The tectorial membrane, Reissner's membrane, limbus, stria vascularis, and spiral ligament appear *normal*.

The sensory epithelium of the saccule is flattened (Fig. 6). The supporting cells are shrunken and there is a loss of about *half of the hair* cells. The otolithic membrane is atrophied and displaced toward the posterior *margin* of the macula.

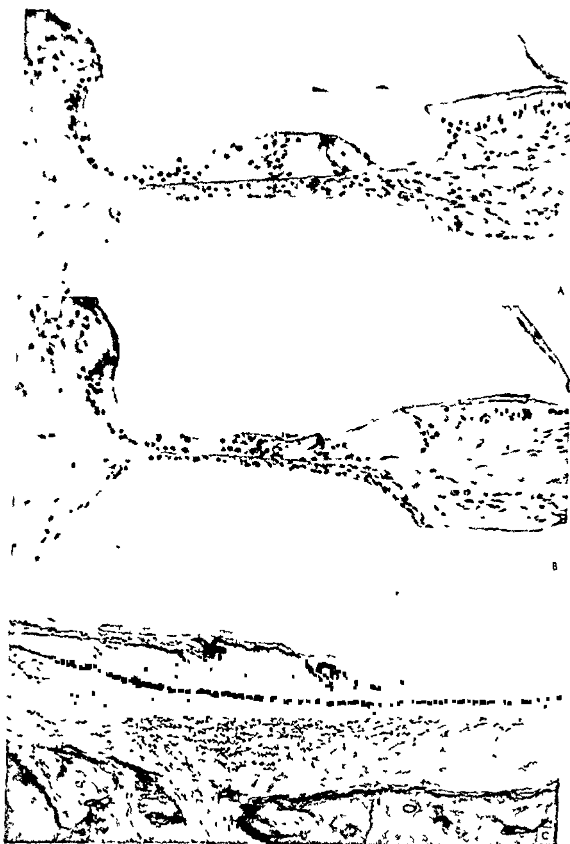


Fig. 2. Mrs. A. P. Sudden deafness due to viral labyrinthitis. (A) Normal organ of Corti in opposite normal hearing ear. (B) Shrunken organ of Corti and tectorial membrane with decreased hair cell population in the involved ear. (C) The saccular wall is ruptured, collapsed and adherent to the underlying shrunken otolithic membrane. The macula is totally devoid of hair cells although supporting cells are present.



Fig. 4. Saccule of old deaf cat. (A) The epithelium of the saccule is disorganized, about 50% of the hair cells are missing and some of the supporting cells are swollen and missing. (B) Epithelium of the saccular macula of a normal animal for comparison.

The saccular nerve appears normal. The macula utriculi and cristi appear normal.

The findings are nearly identical in the right and left ears.

(c) Old man. Mr. N. C., born August 25, 1876, died of carcinoma of the hypopharynx on April 2[illegible], 1962 at the age of 85. During World War I he contracted malaria, was given quinine medication, and noted tinnitus and hearing loss. He believed that his hearing never returned to normal after that time. By occupation a [illegible]gist, he taught for many years at a leading university and apparently had no difficulty in communicating with his students. He never wore a hearing aid or consulted a physician about his hearing, although his wife stated he had some difficulty hearing in noisy places or in a crowd. The patient's wife and

22.7mm

HAIR CELLS

STRIAL ATROPHY

SPIRAL GANGLION CELLS

DISTANCE

CRISTAE

SUP LAT POST

NORMAL NORMAL NORMAL

MACULAE

UTR SAC

NORMAL 50%

A

B

Fig. 3. Old deaf cat. Graphic reconstruction of the cochlea, spiral ganglion and cochlear neurones and quantitative evaluation of the sensorineural elements reveals almost total *loss of hair cells and spiral ganglion cells. In addition about 50% of the hair cells* are lost in the saccule. Midmodiolar section of the cochlea shows the loss of spiral ganglion cells and advanced atrophic changes in the organ of Corti.

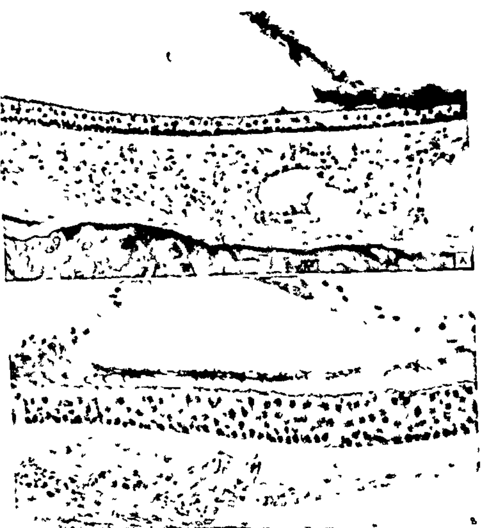


Fig. 6. Old deaf dog. (A) Atrophic epithelium of the saccular macula with 50% loss of hair cells. (B) Normal utricular epithelium in the same ear.

his physician state that his hearing loss became much worse during the last few months of life so that it was difficult to communicate with him.

Examination reveals changes in the cochlea and saccule which differ somewhat from those occurring in the aged cat and dog. The organ of Corti shows moderately severe post mortem autolysis but has good supporting cells and a near normal hair cell population (Fig. 7). There is a severe loss of cochlear neurones (80–90%) in the basal 15 mm of the cochlea (neural presbycusis).

The saccular wall is collapsed and adherent to the macula and the otolithic membrane has degenerated into an amorphous, dark staining mass (Fig. 8). The macula is degenerated severely in one area and elsewhere there is a loss of about 50 percent of the hair cells.

The utricular macula and cristae appear normal.

NORMAL HAIR CELLS
ABNORMAL HAIR CELLS
24.5 mm
HAIR CELLS
STRIAL ATROPHY
GANGLION CELLS
DISTANCE
CRISTAE
SUP NORMAL
HOR NORMAL
POST NORMAL
MACULAE
UTR NORMAL
SAC 50%
A

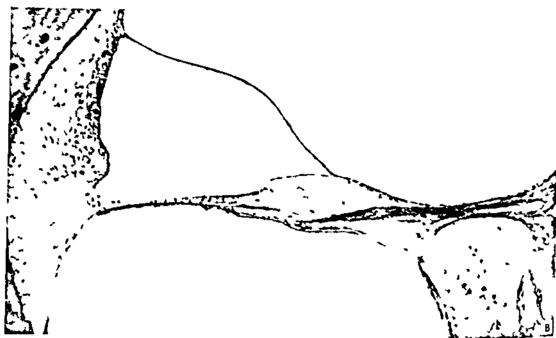


Fig. 5. Old deaf dog. (A) Graphic reconstruction of the organ of Corti and spiral ganglion and estimation of the cell populations reveals a severe loss of hair cells and ganglion cells. There is about 50% loss of hair cells in the macula sacculi. (B) Advanced atrophic changes in the organ of Corti with severe secondary cochlear neuronal degeneration.

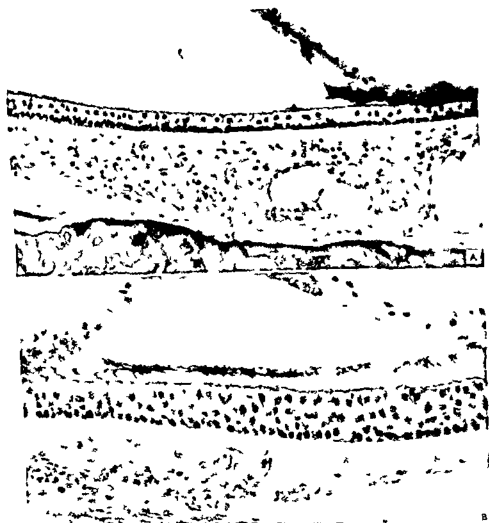


Fig 6 Old deaf dog (A) Atrophic epithelium of the saccular macula with 50% loss of hair cells (B) Normal utricular epithelium in the same ear

his physician state that his hearing loss became much worse during the last few months of life so that it was difficult to communicate with him

Examination reveals changes in the cochlea and saccule which differ somewhat from those occurring in the aged cat and dog The organ of Corti shows moderately severe post mortem autolysis but has good supporting cells and a near normal hair cell population (Fig 7) There is a severe loss of cochlear neurones (85 90%) in the basal 15 mm of the cochlea (neural presbycusis)

The saccular wall is collapsed and adherent to the macula and the otolithic membrane has degenerated into an amorphous dark staining mass (Fig 8) The macula is degenerated severely in one area and elsewhere there is a loss of about 50 percent of the hair cells

The utricular macula and cristae appear normal

NORMAL HAIR CELLS
ABNORMAL HAIR CELLS
24.5mm
HAIR CELLS
% DEST
STRIAL ATROPHY
%
GANGLION CELLS
% DEST
DISTANCE
CRISTAE
SUP
HOR
POST
NORMAL
NORMAL
NORMAL
MACULAE
UTR
SAC
NORMAL
50%
A

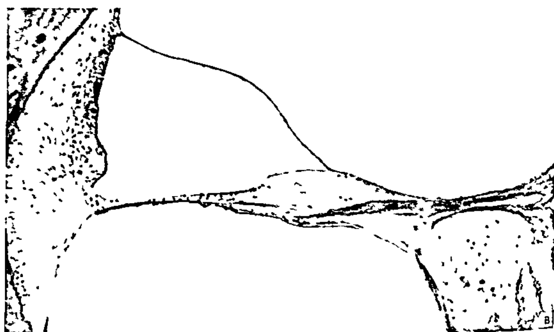
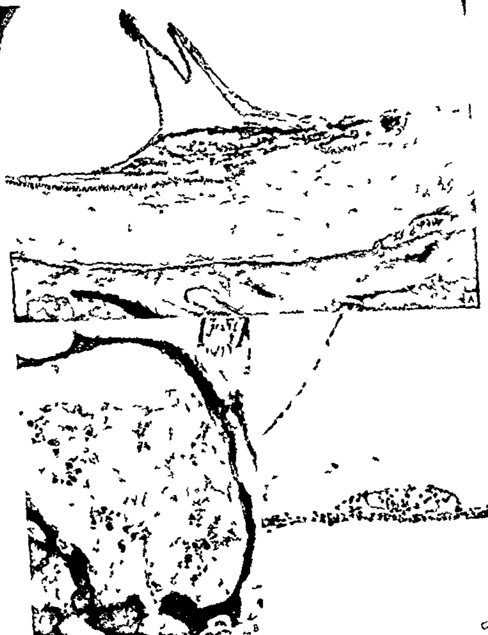
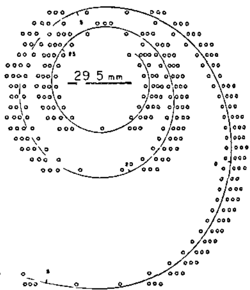


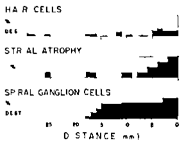
Fig. 5 Old deaf dog (A) Graphic reconstruction of the organ of Corti and spiral ganglion and estimation of the cell populations reveals a severe loss of hair cells and ganglion cells. There is about 50% loss of hair cells in the macula sacculi. (B) Advanced atrophic changes in the organ of Corti with severe secondary cochlear neuronal degeneration.

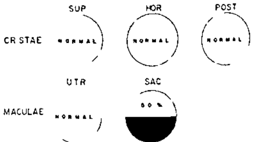


F... Old deaf man. Graph... n tru... n of the *senso...* and neural e ements reveals a ... g)t lo s of ha r ... lls n ... e lo... *er basal turn* but a se ere loss of spiral gangl o... s ... ug ... ut ... e ... er lo... of the co... lea. Th re s a loss of about 50 % of the ... cell ... n ... e ma ula sac uli. A n dmod olar sect on shows the degenera ed co hlear n ur ne

Fig. 8. Old deaf ... A. The wall of the sac ule is collap ed and adherent to a degen... a e ... ol ... e ... b ane. There s d srupt on of the ep thel um in one area and a loss ... bou 50 ... of ha r c lls ... r ugl out the ... e saccule. B. Rosen hal s canal n the ... eg n sl ow ng se ... re loss of coc lear neurones. C. O gan of Corti sl ow ng post... ort ... autoly s but dentifiable ha r cells n the 10 mm r g on

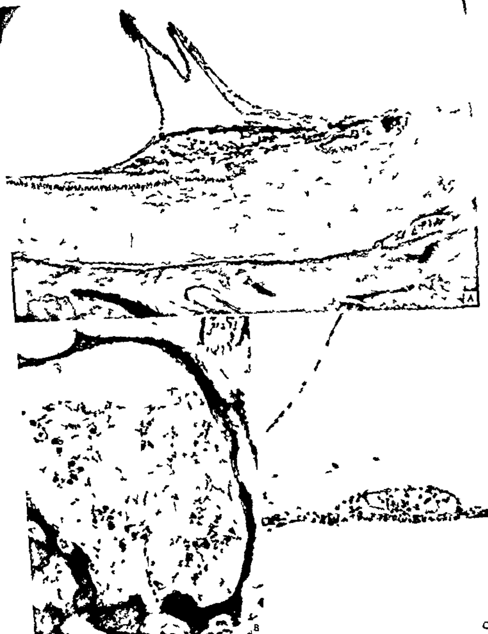

29 5 mm


HA R CELLS
STR AL ATROPHY
SP RAL GANGLION CELLS
D STANCE mm)


SUP
HOR
POST
CR STAE
NORMAL
NORMAL
NORMAL
UTR
SAC
MACULAE
NORMAL

A

1B



F.g. Old deaf man. Graphic reconstruction of the sensory and neural elements reveals a very slight loss of hair cells in the lower basal turn but a severe loss of spiral ganglion cells throughout the lower 15 mm of the cochlea. There is a loss of about 50% of the hair cells in the macula sacculi. A mid-modiolar section shows the degenerated cochlear neurons.

F. 8. Old deaf man. (A) The wall of the saccule is collapsed and adherent to a degenerated otolithic membrane. There is disruption of the epithelium in one area and a loss of about 50% of hair cells throughout the entire saccule. (B) Rosenthal's canal in the 10 mm region showing severe loss of cochlear neurones. (C) Organ of Corti showing post mortem autolysis but identifiable hair cells in the 10 mm region.

Phylogenesis of the Labyrinth

The phylogenesis of the labyrinth as described by Guggenheim (22) may be summarized as follows.

(1) During the Paleozoic period (about 390 million years ago) the primitive lateral line system differentiated into a single semicircular canal and the statocyst into the first utricle. This form of ear may be studied today in the hag fish.

(2) Subsequent transformations consisted of the formation of a second and third semicircular canal and from the utriculus an outpouching with its own nerve which became known as the sacculus.

(3) As life became more complex, a more accurate mechanism of sensing sound waves became necessary and, during the Devonian period, the sacculus developed an outpouching termed the lagena cochleae. The lowest form today showing the lagena is the sturgeon. The lagena is supplied with its own nerve endings and, apparently serves as a sound receptor.

(4) During the Mesozoic period (around 215 million years ago) the pars basilaris developed from the wall of the lagena cochleae and continued to grow in length and finally coil into the definitive cochlea of mammals.

Although the entire labyrinth is exposed equally to aging, metabolic disturbances, and viral attack, the phylogenetically older pars superior (utricle and canals) is rarely affected. It seems reasonable to believe that some phylogenetically determined factor predisposes the younger pars inferior (cochlea and saccule) to degenerative change.

In demonstrating a greater susceptibility to injury, the pars inferior abides by the biological rule that the phylogenetically newer systems in an organism generally exhibit a distinctly greater susceptibility to abuse than do older systems. For example, in the central nervous system, the neopallium is more easily damaged by anoxia than is the archipallium.

RÉSUMÉ

Une dégénérescence cochléo sacculaire peut être provoquée par (1) la surdité congénitale, (2) une labyrinthite virale acquise par suite de naissance et (3) la presbyacousie. La susceptibilité parallèle de l'organe de Corti et du saccule envers ces troubles divers semble indiquer qu'ils ont une embryologie, biologie et cytochimie similaire.

ZUSAMMENFASSUNG

Degenerative Veränderungen im Bereich der Schnecke und des Sacculus werden als Folge von (1) angeborener Taubheit, (2) postnataler Virus labyrinthitis und (3) Presbyakusie angetroffen. Die gleichartige Empfindlichkeit gegenüber diesen Noxen weist auf embryologische, biologische und cytochemische Ähnlichkeiten des Cortischen Organs und des Sacculus hin.

REFERENCES

1 SCHEIBE, A., 1891 2 Ein Fall von Taubstummheit mit Acusticusatrophie und Bildungsanomalien im hautigen Labyrinth beiderseits *Z Ohrenh* 22 11 21

2 — 1895 A histological contribution to deaf mutism due to otitis interna *Arch Otolaryng (Chic)* 24 280–289

3 MARX, H., 1926 Die Missbildungen des Ohres In Wittmaack K (editor) *Handbuch der spe iellen pathologischen An tomie und Histologie* chap 7 Berlin Springer Bd 12 p 669 683

4 LURIE, M H., 1948 The membranous labyrinth in the congenital deaf Collie and Dalmatian dog *Laryngoscope* 58 2?3 287

5 LINDSAY J R., CARRUTHERS, D G., HEMENWAY W G., and HARRISON S., 1953 Inner ear pathology following maternal rubella *Ann Otol* 62 1201 1218

6 HUDSON W R., and RUBEN R J., 1962 Hereditary deafness in the Dalmatian Dog *Arch Otolaryng (Chic)* 75 213 219

WILSON T G., and KANE F., 1959 Congenital deafness in white cats *Acta Otolaryng (Stockh)* 50 269 2 5

8 LURIE, M H 1939 Studies of the waltzing guinea pig *Laryngoscope* 49 558 565

9 — 1941 The waltzing (circling) guinea pig *Ann Otol* 50 113 128

10 — 1942 The degeneration and absorption of the organ of Corti in animals *Ann Otol* 51 712 717

11 FISCH L., 1959 Deafness as part of an hereditary syndrome *J Laryng.* 73 355–382

12 ORMEROD F C., 1960 The pathology of congenital deafness *J Laryng* 74 919 950

13 WARD P H., KINNEY C E., and LINDSAY J R., 1962 Inner ear pathology in congenital deafness *Laryngoscope* 72 435–455

14 LINDSAY J R., 1954 Inner ear pathology due to measles *Ann Otol* 63 754 771

15 VAN DISHOECK H A E., and BIERMAN TH A., 1957 Sudden perceptive deafness and viral infection *Ann Otol* 66 963 980

16 LINDSAY J R., 1959 Sudden deafness due to the virus infection *Arch Otolaryng (Chic)* 69 13 18

17 LINDSAY J R., DAVEY P R., and WARD P H., 1960 Inner ear pathology in deafness due to mumps *Ann Otol* 69 918 935

18 SCHUKNECHT H F., BENITEZ, J., BEEKHUIS J., IGARASHI M., SINGLETON G., and RUEDI L., 1962 The pathology of sudden deafness *Laryngoscope* 72 1142 1157

19 ALTMANN F., 1950 Histologic picture of inherited nerve deafness in man and animals *Arch Otol ryng (Chic)* 51 852

20 SCHUKNECHT H F., 1964 Further observations on the pathology of presbycusis *AMA Arch Otolaryng (Chic)* (In Press)

21 SAUNDERS W H., and LIPPY W H., 1959 Sudden deafness and Bell's palsy A common cause *Ann Otol* 68 830 837

22 GUGGENHEIM L., 1948 *Phylogenesis of the Ear* Murray and Gee Inc., Culver City Colorado pp 15–27

Address (see page 151)

DISCUSSION

F Altmann When examining a great number of human temporal bones in inherited deafness one finds two types of histological changes

First a degenerative atrophy of the *cochleo-saccular portion* similar to that observed in deaf rodents with and without locomotor anomalies Second changes which were called posthydropic neuroepithelial changes by Wittmaack and were found in many temporal bones of deafmutes by Steurer The question arises

whether the so-called posthydropic changes are always caused by viral labyrinthitis or if they are not sometimes due to primary changes of developmental nature in the stria vascularis.

This assumption is supported by the findings of typical posthydropic neuroepithelial changes in Mondini malformation of the cochlea. I would furthermore ask Dr. Schuknecht about the significance of the calcified concrements in the stria vascularis in the slides of the deaf dog. They are quite common in cases of inherited deafness but also occasionally found in patients without a history of hearing loss.

H. A. E. v. Dishoeck: In 200 patients suffering from sudden perceptive deafness and also in a large family suffering from hereditary progressive perceptive deafness the same pattern of cochlear degeneration was found: loss of high tones in mild cases, partly additional middle tone loss in advanced cases and a residual low tone hearing in severe cases. This points to a similar susceptibility of the organ of Corti in both conditions. However, in patients suffering from sudden perceptive deafness due to a vascular accident, the same pattern is found which fact—being the result of totally different pathology—needs explanation.

J. L. Desmedt: I am very interested in Dr. Schuknecht's view that the innervation of the cochlea may be largely preserved in human congenital deafness while it undergoes degeneration in acquired deafness. Albino cats with congenital deafness also disclose a pathological cycle which destroys the organ of Corti but only involves the nerve cells in the spiral ganglion to a limited extent and after a considerable latent period (Fraser, 1924; Howe, 1935; Citron, Exley & Hallpike, 1956; Wilson & Kane, 1959). The following physiological observations made recently in my laboratory further suggest that the efferent innervation to the cochlea may also be preserved in this condition.

We studied a male adult albino cat who had one eye blue and the other green. Polydactylia was present, there being six digits in each paw. The eardrums were clean and translucent. The middle ear exposed surgically through the acoustic bulla did not present any sign of infection nor any pathological process. The cat was anesthetized with α-chloralose and fitted into the Horsley-Clarke frame for insertion of stereotaxic electrodes into the crossed olivo-cochlear bundle on the midline of the brainstem (cf. Desmedt, 1962). On recording from auditory structures no response whatsoever was evoked by acoustic stimulation with clicks even 80 dB above the threshold of normal cats tested under identical conditions. The platinum wire electrodes placed on the right or left round window membranes failed to pick up any microphonic or neural potential.

We then wondered about the status of the efferent innervation. The activity of the olivo-cochlear system is usually demonstrated by its inhibitory effect on auditory nerve response to sound. This effect could not be shown in such a deaf cat with no acoustic evoked potentials. However, we discovered that single electric pulses delivered to the crossed olivo-cochlear bundle were followed after a brief latency by an electrical sign recordable at the round window. A pulse of 3 volts elicited a negative-going potential of about one millivolt (Fig. 1 A). A pulse of 15 volts elicited a larger potential which was followed by a slower wave (B) better shown in the record registered with a slower time base (C). These potentials are thought to represent some kind of electrical activity involving inner ear structures because it was clearly separate from the shock artifact, it appeared with a definite threshold (about 1.5 volts) and did not change its

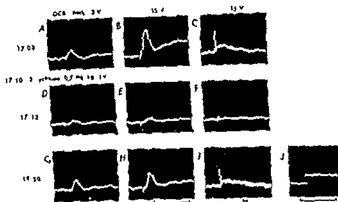


Fig. 1. Cat A 416, 3.4 kg, anesthesia with α-Chloralose, muscle paresis with Flaxedil. Cathode ray oscillograms of potentials recorded from the round window membrane (negativity upwards) at the times indicated on the left side. First row of records: potentials evoked by an electric shock of 3 volts delivered to the decussation of the crossed olivo-cochlear bundle in the medulla. Second row, electric shocks of 15 volts. Third row, same recorded on a slower time base. Horizontal calibration 3 milliseconds. Vertical calibration step of one millivolt in J.

configuration on reversing the shock polarity. Our experimental conditions and the histological controls exclude spurious antidromic activation of fibres belonging to the auditory nerve.

Strychnine sulphate was injected into this cat because it is known to antagonize olivo-cochlear inhibition (Desmedt & Monaco, 1961). This caused a marked and prompt depression of the potentials recorded at the round window, for the two shock intensities tested (Fig. 1 D–F). The strychnine effect was slowly reversible. About two hours later the same stimulations elicited potentials which were not unlike those recorded before strychnine.

Strychnine at the dose used is not supposed to block conduction of the action potential in nerve fibres. Therefore it seems reasonable to believe that our strychnine-sensitive potentials depended on synaptic interaction between the two neural components of the inner ear, and could represent post-synaptic inhibitory potentials elicited by activated olivo-cochlear terminals in the membrane of auditory dendrites. In the cat the close anatomical relation of these two components at the base of hair cells make such an interaction at least plausible (cf. Desmedt & Monaco, 1961, Spoendlin & Gacek, 1963). The likeliness of hair cell participation in the phenomenon recorded is played down in such a case of congenital deafness in view of the degeneration and distortion disclosed by the sensory cells.

Firm and far reaching conclusions should not be based on a single observation. Nevertheless, our data suggest that efferent olivo-cochlear axons may be excitable and functional in congenital deafness and they emphasize the potential interest of such cases for the analysis of synaptic interactions within the inner ear.

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COCHLEAR DAMAGE FROM OTOTOXIC ANTIBIOTICS

HANS ENGSTRÖM and AARNO KOHONEN
Goteborg Sweden and Helsinki, Finland

From the Ear Nose and Throat Departments of the Universities of Goteborg (Head Prof G Herberts) and of Helsinki (Head Prof U Sirala)

This short report is preliminary to an extensive one to be published in short as a thesis by A Kohonen It deals with the pattern of degeneration in both sensory *cells and neural elements* in the organ of Corti after administration of ototoxic antibiotics It is shown how the pattern of degeneration can be studied with newly *developed techniques and the* principles according to which the degeneration takes place are described

The ototoxic *effect of antibiotics belonging to the streptomyces group,* has been widely studied both from a clinical and an experimental point of view Their devastating effect on hearing and equilibrium has constituted an important clinical problem and the development of new antibiotics within related groups has made it necessary to make it a routine to study possible ototoxic effects *During the last decade a considerable literature has been* published within this field and although a few authors have found vascular *and central neural changes, the consensus of opinion among most authors seems to be that at least the primary damage to hearing is depending upon* a degeneration in the organ of Corti and its sensory receptors Several authors have also reported on degeneration within the spiral ganglion but very little pertinent information can be found regarding the fate of nerve fibers and nerve endings inside the organ of Corti itself This gap in our knowledge is most amazing as one of the central problems in the discussion on the ototoxicity of antibiotics has been and still is if the primary damage is on the sensory receptor level or if it has a more central location

Neomycin and kanamycin *are the drugs most intensely studied during* the last years (Olivieri & Rossi, 1958, Beck & Krahl, 1962, Darrouzet, 1963) *In* a recent paper Hawkins & Engstrom (1964) studied the pattern of cochlear sensory cell degeneration in guinea pigs injected with repeated doses of kanamycin The major aim of the present paper is to study and compare the toxic *effect on cochlear sensory cells and nerve fibers of several* related antibiotics By the application of special techniques developed at the Ear Nose and Throat Department in Goteborg it has become possible to make an exact recording of sensory cell loss and nerve fiber loss within considerable stretches of the organ of Corti

References

CITRON, L., EXLEY, D., and HALLPIKE, C. S., 1956: *Brit. Med. Bull.*, *12*, 101-104.
DESMEDT, J. E., and MONACO, P., 1961: *Nature*, *192*, 1263-1265.
DESMEDT, J. E., 1962. *J. Acoust. Soc. Amer.*, *34*, 1478-1496.
FRASER, J. S., 1924. *J. Laryng.*, *39*, 29-31.
HOWE, H. A., 1935: *J. Compar. Neurol.*, *62*, 73-79.
SCHUKNECHT, H. H., and GACEK, R., 1963: *Ann. Otol.*, *72*, No. 3, 660-686.
WILSON, T. G., and KANE, F., 1959: *Acta Otolaryng. (Stockh.)*, *50*, 269-275.

E. Bocca: I should like to know from Dr. Schuknecht if the fact that cochlea and saccule are both pertaining to a more recent phylogenetical age and the fact that they very often show a parallel pathology in several degenerative conditions may point to the possibility that the cochlea and sacculus may also represent a physiological unit. The problem of saccular hearing is raised again by the beautiful work of Schuknecht. The only thing which is somewhat conflicting with this so-called parallelism between cochlea and sacculus is their different innervation, the former receiving a cochlear and the latter a vestibular innervation, which makes a difference between their relative phylogenetic ages.

F. Schuknecht (Reply): I am glad to learn from Dr. *Altmann* that there are two types of hereditary deafness, one with loss of tissue substance and the other characterized by a clumping or agglutination of the sensory structures without loss of cells. The latter condition has been termed hydropic degeneration when seen in certain other disorders and it is often difficult to differentiate from fixation artefact and *post mortem* degeneration. He suggests that the changes occurring in some ears with genetic type cochleo-saccular degeneration may be entirely the result of dysgenesis of the stria vascularis. This may be true for I believe the saccule could derive metabolic support from the stria vascularis.

Prof. *van Dishoeck* has had a rich experience in the clinical manifestations of sudden deafness and has shown, indeed, that many cases of sudden deafness probably are of viral etiology. We have examined the ears of four patients with sudden unilateral deafness and found changes similar to those occurring in ears sustaining from known viral attack. Three of these ears were from our laboratory and one from the laboratory of Prof. Ruedi. We interpreted the pathology as representing the effects of viral labyrinthitis and not of vascular occlusion or hemorrhage.

Prof. *Bocca* has "brought an old skeleton out of the closet". Specifically he asks whether the evidence presented does not support the idea that the saccule plays an auditory role. In this regard I have only one bit of evidence to report. Animals which have been behaviorally conditioned for auditory threshold testing and in which severe cochlear lesions are made are totally unresponsive to auditory stimulation at high intensities even though they have normal saccules. Thus it would seem that the saccule does not respond to air conducted acoustic stimuli



Fig. 2. Nerve endings and nerve fibers in guinea pig cochlea. The "tuliplike" form of the nerve endings (NE) is very characteristic. This long type of stalks on the nerve endings indicates that the specimen is from the upper part of the cochlea. At the lower end they are much shorter. The complicated course of the *outer spiral bundle (OSB)* is evident. A few radiating tunnel fibers can be seen although the larger number of these are out of focus. Magnification 750 ×.

described by Engstrom, Ades and Hawkins and by Hawkins and Engstrom. For the demonstration of nerve fibers and nerve endings we have modified Maillet's method (Figs. 2 and 3) with osmium tetroxide–zinc iodide and it can now be used with excellent results for light and/or electron microscopy. To a large extent we have used surface preparations or embeddings in acrylate and epoxy resin instead of celloidin embedding. This permits a simultaneous sectioning of specimens for light and electron microscopy.

RESULTS

Ototoxic antibiotics of the streptomyces group used in this study all follow a very similar pattern in their damaging effect on cochlear cellular structures. By the use of the surface specimen technique and phase contrast microscopy it is possible to study the normal pattern of cellular arrange-



Fig. 1. Normal pattern of outer hair cells from the rabbit cochlea. The hair cells form three distinct rows (1, 2, 3) and between the cells the supporting cells can be seen. The phalangeal form of the slender processes of the first row of Deiters' cells is very characteristic. Magnification 1750 ×.

MATERIAL

In our study guinea pigs have been used and groups of animals have been injected with (*a*) Kanamycin, (*b*) Neomycin, (*c*) Framycetin.

In total the number of animals injected has been 64 and the injected antibiotic has been given in a dose increasing from a small one to a large dose. The animals have been sacrificed in a carefully planned way regarding survival time. All these data will be published in an extensive report on the experiments by A. Kohonen. As they are of secondary importance for the present paper the interested reader is referred to the more extensive report to be published within short.

METHODS

During the last decade we have devoted a considerable time to a study of new techniques for an exact registration of cochlear damage both on sensory receptor and nerve fiber–nerve-termination level. These techniques will be subject to a thorough description in a monograph, under preparation by Engstrom, Ades & Andersson. In the present study we have used a surface specimen technique (Fig. 1) for the study of sensory cell loss as

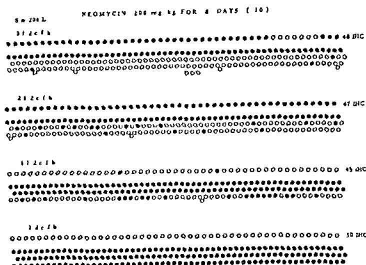


Fig. 4. Cochleogram from a guinea pig that has received 200 mg neomycin/kg body weight for 8 days and been sacrificed 10 days after the last injection. The black dots indicate damaged cells and the typical pattern of degeneration at a severe damage is very distinct. At the basal end of the cochlea all outer hair cells have been damaged. In the second coil the two first rows of outer hair cells have been lost. The inner hair cells are on the contrary, most damaged at the top of the cochlea.

the cells belonging to the basal coil and the innermost row of outer hair cells all through the cochlea are earlier damaged than cells belonging to the second and third row at the top. In the second coil from the base the third row of outer hair cells is less vulnerable than the first and second row. This principle of degeneration of outer hair cells is very clearly seen in the cochleogram of Fig. 4 where the dark dots indicate damaged cells.

The inner hair cells are much later damaged than the outer ones. Here a most interesting thing has been found. While the outer hair cells first are damaged at the basal end, the inner hair cells are earlier damaged at the top coil of the cochlea as can be seen in Fig. 4. This is not a unique finding in this case, but found as a recurring phenomenon in almost every case and with all the three antibiotics used.

In the cochleograms only cells are registered where the damage to the cells is considerable. In the surface specimen it is possible to follow the different stages in the degeneration and the formation of "collapsed cells". This will be further described by Kohonen and by Engström, Ades and Andersson but a few different types can be seen in Fig. 3.

The ototoxic effect of the antibiotics used has a damaging effect upon the sensory cells, but with increasing dosage considerable damage appears also in the supporting elements. This has been studied both by surface specimen technique and by light and electron microscopy of sectioned material. In the sections, however, it is often very difficult to define to

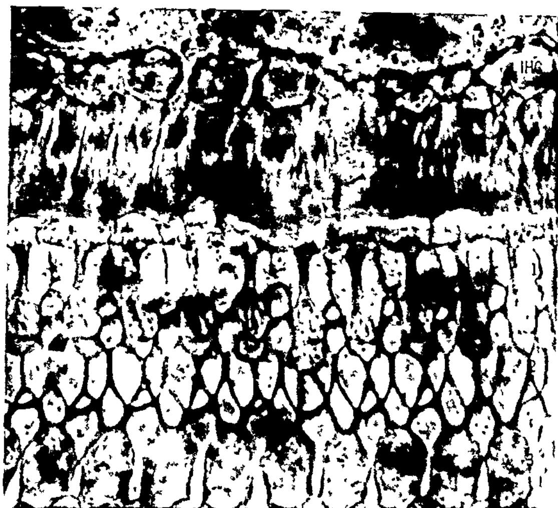


Fig 3 Severely damaged cochlea 2½ coils from the base from a guinea pig that has been injected with kanamycin 400 mg/kg body weight for 8 days and been sacrificed 14 days after the last injection The most extensive damage is seen in the first (1) and second (2) row of outer hair cells There are also some damaged inner hair cells (IHC) Magnification 1450 ×

ment in the cochlea (Fig 1), and also to register a loss of even one single cell or groups of cells In the report by Hawkins and Engström the general tendency in the pattern of outer hair cell loss could be described In the present study comprising a very large material of normal and pathologically altered cochleas it has been clearly shown that the outer hair cells at the basal end of the cochlea are first damaged by all the three antibiotics used First only occasional cells start to degenerate, then groups of cells disappear and finally all the three rows of cells in the basal coil are damaged This follows a very clear cut principle according to increasing dosage and survival time In the basal coil there is a slight but not pronounced difference in vulnerability between the cells of the three outer hair cell rows, the first row being more sensitive and the further we follow the degeneration towards the top of the cochlea, the more pronounced becomes the difference between individual cellular rows As can be seen in the cochleogram (Fig 4)

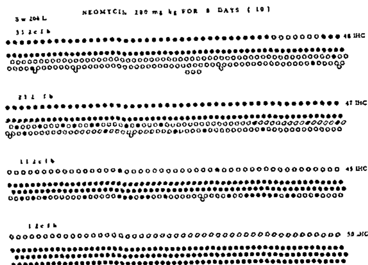


Fig 4 *Cochleogram from a guinea pig that has received 200 mg neomycin/kg body weight for 8 days and been sacrificed 10 days after the last injection* The black dots indicate damaged cells and the typical pattern of degeneration at a severe damage is very distinct At the basal end of the cochlea all outer hair cells have been damaged In the second coil the two first rows of outer hair cells have been lost The inner hair cells are on the contrary most damaged at the top of the cochlea

the cells belonging to the basal coil and the innermost row of outer hair cells all through the cochlea are earlier damaged than cells belonging to the second and third row at the top In the second coil from the base the third row of outer hair cells is less vulnerable than the first and second row This principle of degeneration of outer hair cells is very clearly seen in the cochleogram of Fig 4 where the dark dots indicate damaged cells

The inner hair cells are much later damaged than the outer ones Here a most interesting thing has been found While the outer hair cells first are damaged at the basal end the inner hair cells are earlier damaged at the top coil of the cochlea as can be seen in Fig 4 This is not a unique finding in this case, but found as a recurring phenomenon in almost every case and with all the three antibiotics used

In the cochleograms only cells are registered where the damage to the cells is considerable In the surface specimen it is possible to follow the different stages in the degeneration and the formation of "collapsed cells" This will be further described by Kohonen and by Engstrom, Ades and Andersson but a few different types can be seen in Fig 3

The ototoxic effect of the antibiotics used has a damaging effect upon the sensory cells but with increasing dosage considerable damage appears also in the supporting elements This has been studied both by surface specimen technique and by light and electron microscopy of sectioned material In the sections, however, it is often very difficult to define to

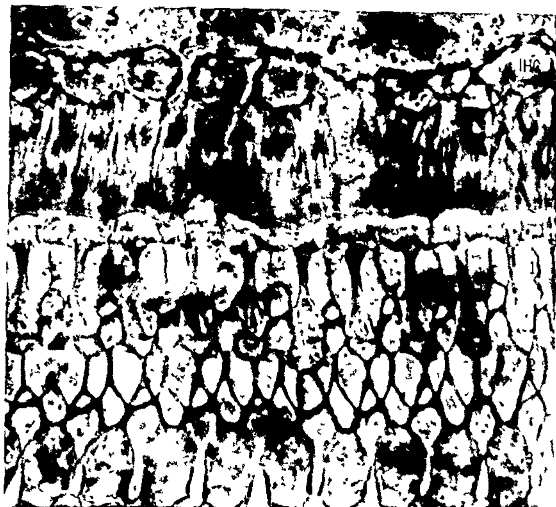


Fig. 3. Severely damaged cochlea 2½ coils from the base from a guinea pig that has been injected with kanamycin 400 mg/kg body weight for 8 days and been sacrificed 14 days after the last injection. The most extensive damage is seen in the first (1) and second (2) row of outer hair cells. There are also some damaged inner hair cells (IHC). Magnification 1450×

ment in the cochlea (Fig. 1), and also to register a loss of even one single cell or groups of cells. In the report by Hawkins and Engstrom the general tendency in the pattern of outer hair cell loss could be described. In the present study comprising a very large material of normal and pathologically altered cochleas it has been clearly shown that the outer hair cells at the basal end of the cochlea are first damaged by all the three antibiotics used. First only occasional cells start to degenerate, then groups of cells disappear and finally all the three rows of cells in the basal coil are damaged. This follows a very clear cut principle according to increasing dosage and survival time. In the basal coil there is a slight but not pronounced difference in vulnerability between the cells of the three outer hair cell rows, the first row being more sensitive and the further we follow the degeneration towards the top of the cochlea, the more pronounced becomes the difference between individual cellular rows. As can be seen in the cochleogram (Fig. 4)

coils, using electron microscopy and Hilding & Wersall (1962) could show by application of the Koelle technique and electron microscopy that there is a spatial difference in the distribution of the nerve endings of different sizes at the outer hair cells It is very clear that there are not two types of sensory cells or innervations but a gradient of large endings and medium large or small ones This will be extensively discussed by Engstrom, Ades and Andersson

If large doses of antibiotics are administrated the degeneration often is so extensive that only rests of the nerve endings and nerve fibers can be seen In these specimens with extensive damage the spironeurons are still often present and can be followed over long stretches of the organ of Corti In these specimens details in the connection between these spironeurones and sensory cells may be studied in detail By the application of our nerve stain and electron microscopy a specifique staining of the granulated endings can be achieved The application of the methods used in this study will simplify further studies on the olivocochlear bundle and the efferent innervation of the cochlea

RESUME

Il est possible de definir et preciser l effet ototoxique de certains antibiotiques par des methodes employees dans ce travail L expansion et la forme de la destruction des cellules et des nerfs dans l organ de Corti chez des animaux traites avec certains antibiotiques suit des principes très clairs et la destruction cellulaire et la degeneration des nerfs est très systematique La distribution de la degeneration peut etre simplement enregistree dans «le cochleogram» Les resultats des methods peuvent etre traites par l analyse mathematique moderne

ZUSAMMENFASSUNG

Umfassende Forschungen in der Entwicklung von leichten, sicheren und reproduzierbaren Techniken welche der Untersuchung von cochlearen Schaden dienen haben zu neuen Methoden fur die Darstellung von Sinneszellen und Nervenfasern gefuhrt Diese Methoden wurden zur Untersuchung der Ausdehnung und Form der Zellzerstorung und Nervendegeneration im Cortischen Organ von Tieren angewandt die mit verschiedenen ototoxischen Antibiotika behandelt worden waren Die Untersuchungen zeigten dass der Verlauf der Schadigung seinen klaren Prinzipien folgt und im Verhaltnis der Zellzerstorung und Nervendegeneration sehr systematisch ist Im Cochleogramm konnen die Verteilung der zellularen Schaden auf einfache Weise registriert und die verschiedenen Versuchstiere leicht miteinander verglichen werden Es zeigte sich dass die Art der angewandten Techniken ein weites Feld und grosse Moglichkeiten fur verwandte Gebiete offnet Die Methode kann ebenso fur die Computeranalyse angewandt werden

REFERENCES

Bi k Cui and Knaul P 1962 Experimentelle und feingewebliche Untersuchungen uber die Ototoxicitat von Kanamycin *Arch Ohr Nas Kehlkopfheilk* 1 2 594–610



Fig. 5. Nerve stained specimen showing the pattern of innervation in a cochlea damaged by neomycin. The inner spiral bundle (*ISB*), the spiral tunnel bundle (*STB*) the radiating tunnel fibers (*RTF*) are rather distinct while the framework of fibers at the outer hair cells is partly destroyed. This animal has received neomycin 200 mg/kg body weight for 8 days and been sacrificed 10 days after the last injection. Magnification 800 ×

which row a cell that is left belongs and that may account for the disagreement found in literature dealing with the pattern of degeneration.

The nerve staining technique used in the present study gives an extremely clear and distinct picture of the innervation of the organ of Corti both in direct observation of surface specimens with ordinary light or phase contrast microscopy and in sectioned material (Fig. 2). Under the influence of ototoxic antibiotics it can be found that a considerable damage to neural elements starts soon after the damage to sensory cells. This degeneration starts as an irregular collapse and disintegration of nerve endings under the hair cells as can be seen in Fig. 5. With increasing dosage and survival time the degeneration will be extensive and clumps of neural matter replace some of the delicate fibers while others completely disintegrate and disappear.

The pattern of neural degeneration follows to a large extent the same system as has been found for sensory cell degeneration. In this connection it stands out very clearly that the cellular loss after administration of antibiotics first strikes cells which are provided with large granulated nerve endings. In 1958 Engstrom could demonstrate a spatial difference in the innervation of sensory cells in the cochlea. Smith & Sjostrand (1961) could further show a difference between the basal end of the cochlea and upper

SLOW CORTICAL RESPONSES EVOKED BY ACOUSTIC STIMULI[1]

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Evoked responses of the waking human brain to acoustic stimuli can easily be recorded from external electrodes by means of an average response computer. The clearest responses are anatomically diffuse (strongest from frontal and vertex), long in latency, and are evoked by visual or tactile as well as auditory stimuli. Their amplitude varies quite widely across subjects, with the state of the subject, with the interval between stimuli (up to 10 seconds), and from one individual stimulus to the next. The average of a set of successive responses is sufficiently related to the intensity of the stimulus, however, to make the method useful for objective audiometry on a purely empirical basis, even though the response does not arise from the primary auditory cortical area.

Our thresholds of detection of the average evoked responses of fifty severely hard-of-hearing children 7 to 16 years old were compared with the children's subjective thresholds for the same filtered clicks. The mean difference was only 2.5 dB. The averages for five frequencies diverged by 18 dB or more in only two cases. The relation to their pure tone thresholds, as determined in our clinic, was almost equally close.

Characteristics of the Evoked Responses

Electrical responses to acoustic stimuli may be recorded from the vertex of the human head by means of average response computers (Katzman 1964; Davis & Yoshie 1963). One class of these responses, of long latency and slow time course, gives great promise of clinical usefulness in assessing the state of the peripheral auditory system and perhaps also certain parts of the central auditory system. No sleep or sedation is needed and no understanding or voluntary cooperation is required beyond sitting reasonably quiet for a minute or two at a time.

The slow response in question does not arise from muscles like certain fast responses that have been described elsewhere by others (Bickford, Jacobson & Cody 1964; Mast 1963). It does not arise from the auditory projection area of the temporal lobe like the primary evoked responses to anesthetized animals that are used by electrophysiologists and neurosurgeons to map the sensory projection areas. It does arise diffusely from the cerebral cortex over a wide area that is like a cap worn well forward on the

[1] This investigation was supported by Public Health Service Research Grant No. B 3856 from the National Institute of Neurological Diseases and Blindness.

DARROUZET, J, 1963 Essais de protection de l'organe de Corti contre l'ototoxicité des antibiotiques *Rev Laryng (Bord)*, 84, 459–478

ENGSTRÖM H, 1958 On the double innervation of the sensory epithelia of the inner ear *Acta Otolaryng (Stockh)*, 49, 109–118

ENGSTRÖM, H ADES H W, and HAWKINS J E, JR, 1964 Cytoarchitecture of the organ of Corti *Acta Otolaryng (Stockh)*, Suppl *188* 92–99

HAWKINS J E JR, and ENGSTRÖM, H, 1964 Effect of kanamycin on cochlear cytoarchitecture *Acta Otolaryng (Stockh)*, Suppl *188*, 100–107

HILDING, D, and WERSÄLL, J, 1962 Cholinesterase and its relation to the nerve endings in the inner ear *Acta Otolaryng (Stockh)*, 55 205–217

MAILLET, M, 1963 Le réactif au tétraoxyde d'osmium iodure de zinc *Rev Med (Tours)* 4, 247–268

OLIVIERI, A and ROSSI G, 1958 Ricerche sperimentali sul potere antibatterico e sugli effetti a carico delle strutture cocleovestibolari di un nuovo sale di neomicina il glucuronato di neomicina *Minerva Otorinolaring* 8 Nota I–IV

SMITH C A and SJÖSTRAND F S 1961 Structure of the nerve endings on the external hair cells of the guinea pig cochlea as studied by serial sections *J Ultrastruct Res* 5 523–556

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A Kohonen ENT Department University of Helsinki, Finland

DISCUSSION

H Davis The method described by Dr Engström offers great possibilities for physiological experiments We should be able to determine, for example, (1) whether the threshold for inner hair cells is higher than for external hair cells (2) whether the inner hair cells produce cochlear microphonic (alternating current) potentials or only summating (direct current) potentials, and (3) whether the frequency tuning of the inner hair cells is as sharp as for the external hair cells Also the nature of the external spiral nerve fibers that run for long distances along the organ of Corti can be established Perhaps they are only efferent fibers The engineers who make models for cochlear action and frequency analysis lay great stress on these long spiral "afferent" fibers, and they may be badly misled What is Dr Engström's present opinion on this point?

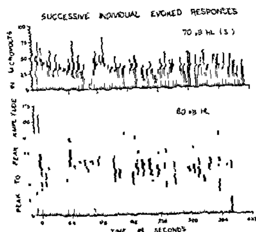


Fig. 2. Unusually large auditory evoked responses could be measured individually in the standard EEG record of one normal subject. The noteworthy feature is the large random variability of amplitude from one response to the next. No cyclic or overall trends are evident. The brief interruptions in the 70 dB series had no consistent effect. Hearing levels are relative to the ISO reference level. The tone pips were 1200 c/s. (From H. Davis and S. Zerlin, "The variability of evoked responses", *The Physiologist*, in press.)

the pass band for the initial electroencephalogram to the range from 0.4 to 35 c/s (half amplitude at these frequencies). The successive improvement in signal-to-noise ratio obtained by increasing the number of responses that are averaged is illustrated in Fig. 1.

The rate of stimulation must be no faster than one every ten seconds to obtain maximal responses. The responses are very small and differ in waveform if the interval is only half a second. This refractory effect operates within each sensory modality, i.e. sound depresses the response to a following sound and touch depresses the response to touch, even when delivered to opposite ears or hands; but touch, audition and vision interact very little with one another.

In general, strong stimuli elicit larger responses but it is difficult to define a precise input-output relation because other factors, notably the state of the subject, whether vigilant or indifferent or habituated or drowsy, is important and also because of the variability of the responses, both across subjects and across successive trials. Typical peak-to-peak voltages in response to fairly loud clicks are of the order of 10 to 20 μv. In rare individuals they may be as large as 100 μv and can be measured individually. Successive responses vary by a factor of two or three and apparently quite at random, as shown in Fig. 2.

The long time-course and the slow recovery of the slow cortical evoked response, its variability, its complex structure, its curious anatomical distribution, and its semi-specific relations across sensory modalities make it impossible as yet to incorporate this response into any plausible scheme of

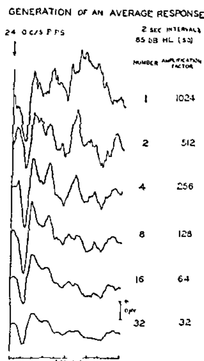


FIG 1 A series of 32 stimuli was interrupted to write out the cumulated sums, as indicated The amplification was adjusted so that the calibration is the same for all of the records Note the progressive elimination of the spurious waves in the latter part of the early records The shrinkage of the average evoked response in the last three lines is due largely to the less frequent pauses for write-out The response after a two second interval averages less than half the voltage of the first response after a long pause In addition this subject regularly shows considerable overall 'habituation' during an experiment Upward deflection indicates vertex more positive relative to earlobe

top of the head Visual and tactile stimuli evoke very similar responses from the same non-specific areas, although there are minor differences from one modality to another and also from one subject to another and perhaps also with age in very young children

The most typical sequence of waves in response to auditory stimuli is a small vertex-positive wave with its peak at about 50 milliseconds followed by a strong vertex-negative wave at 100 milliseconds and then a large vertex-positive wave at 175 milliseconds The final positive wave may be a plateau or show two peaks, as in Fig 1 The latter part of the response may suggest a rhythm, but it is much more variable than the initial positive-negative-positive complex All of our quantitative measurements represent the peak-to-peak voltage from the first negative to the second positive wave We believe that the overall pattern is composed of three or four components which may vary independently in amplitude but which are fairly stable in latency It is this feature of being time-locked to the stimulus that makes it possible to separate the evoked responses from the random EEG background by averaging the electrical output after successive stimuli We also reduce the noise in the final records significantly by restricting

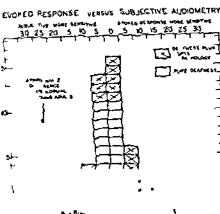


Fig 3

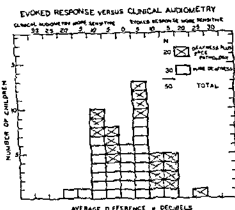


Fig 4

Fig 3 All of the 50 children are educationally deaf but all had clinical audiometric thresholds for at least 250, 500 and 1000 c s. The differences represented here are between the estimated threshold of detection of an evoked response and the subjective threshold of the child listening to the same tone pips. There were no false positive responses in the sense of an evoked response appearing at a frequency for which the child failed to respond voluntarily at all, even though some subjective thresholds were less sensitive than the estimated ER thresholds. The differences measured for each child were averaged algebraically. The histogram shows the distribution of these average differences.

Fig 4 This figure represents the same group of 50 children and evoked response tests as Fig 3. The difference in distribution is due chiefly to the differences in the acoustic stimuli, tone pips (filtered clicks) versus pure tones. Tone pips scatter acoustic energy and are therefore better heard than pure tones by children who have very steep audiograms, either falling or rising. Also the test frequencies differ slightly. The clinical pure tone tests had been done as routine several weeks previously but the results were unknown to the electroencephalographers until after their estimates of evoked response thresholds had been recorded.

congenital atresia of the external ear canals. All of the children who by clinical audiometry failed to hear 1000 c s or higher were identified by the evoked response test without consulting the clinical record, as showing probably only tactile responses' (or none at all).

After quantitative estimates of the evoked response thresholds had been recorded, the voluntary thresholds for the same stimuli were then obtained. The evoked response thresholds were also compared with the most recent clinical pure tone audiometric thresholds on record for the child, disregarding the small differences in the test frequencies employed.

The distribution histogram of the (algebraic) differences between the evoked response and the voluntary subjective thresholds was normal in form (see Fig 3). The extremely deaf children are omitted in these quantitative comparisons. The mean difference for the fifty with best hearing was 2.3 dB, i.e. the child's voluntary response was slightly more sensitive than our detection of the cortical evoked response. This agreement is much

the processing of auditory information. It nevertheless can yield audiometric and perhaps neurological information of real clinical value, but only on a purely empirical basis.

Audiometric Use of Evoked Responses

We have employed the slow cortical evoked response as an end point of "objective" audiometry of severely hard-of-hearing children at Central Institute for the Deaf. Our stimuli are filtered clicks or "tone pips", at five frequencies: 300, 600, 1200, 2400 and 4800 c/s. The pips all reach their maximum amplitude on the third wave and fall off almost as rapidly. Thresholds were determined for normal listeners and compared with their audiograms. This "threshold transfer" allows us to express our attenuator readings as hearing levels, i.e. decibels above the thresholds of an ideal listener whose threshold corresponds to the new International (ISO) 1964 reference zero level at each frequency.

The children sit comfortably reading or are entertained with pictures. Silver disc electrodes are attached at the vertex and either an ear lobe or the mastoid process. Earphones (Philips) with circumaural cushions, rather than a loudspeaker, are regularly employed (except for children below 7 years of age) in order to reduce extra-aural tactile stimulation. Tone pips were delivered every 3.2 seconds and responses summed in blocks of 32. (We now believe that it will be more efficient to employ more frequent stimuli, perhaps at 1 per second, and to collect blocks of 64 responses.) The clarity and the amplitude of the response patterns are noted on the oscilloscope and graphic writeout, and the threshold for each frequency is estimated on the spot by extrapolation or interpolation. Averaged responses at three well-chosen intensities are usually sufficient for a given frequency. Since individual differences in pattern may be considerable, a clear supra-threshold response is required at the beginning of a series. The first trial is therefore regularly made at 1200 c/s and at a hearing level of about 100 dB (ISO). Maximum hearing level available is 126 dB. The entire procedure, including application of the electrodes, for estimating a binaural audiogram for the five frequencies requires about 50 minutes.

We have tested 60 pupils, most of them between 10 and 16 years old, 45 from the Oral Department and 23 from the Speech Pathology Department. All of them are educationally deaf, but the pupils in the Speech Pathology Department have special difficulties in learning in addition to their hearing losses. None of our pupils have pure "congenital sensory aphasia". A few tests were discarded as technically unsatisfactory. Fifty of the children tested had sufficient hearing to give clinical audiometric end points, at least at 250, 500 and 1000 c/s. In only one case did we fail to obtain electrical evoked responses at the two lowest frequencies, but we are not yet certain whether the responses to the loudest sounds were truly auditory or perhaps only tactile. The child who gave no responses whatever his

horsverarbeitung zu Wir hoffen, dass diese Methode uns audiometrische und vielleicht auch neurologische Aufschlusse von wirklichem klinischem Wert vermittelt, aber das muss sich erst auf rein empirischer Basis herausstellen

REFERENCES

BICKFORD R G., JACOBSON, J L., and CODY, D T R., 1964 Nature of average evoked potentials to sound and other stimuli in man *Ann N Y Acad Sci*, *112*, 204–223

DAVIS, H., and YOSHIE, N., 1963 Human evoked cortical responses to auditory stimuli *The Physiologist* 6 164

ENGEBRETSON A M., COX, J R., JR., and GLAESER D H HAVOC, a digital computer for analyzing bio-electric signals *IEEE Transactions on Medical Electronics* (In press)

KATZMAN R., 1964 Sensory evoked response in man *Ann N Y Acad Sci* *112* (cf esp W G Walter pp 320–361)

MAST T 1963 Muscular *vs* cerebral sources for the short latency human evoked responses to clicks *The Physiologist* 6 229

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better than for a control group of young adults for whom the mean difference is between −20 and −25 dB. The scatter in the individual differences is somewhat wider for the children suffering from speech pathology than for those suffering simple, although severe, hearing loss.

For the fifty children the difference between the evoked response thresholds and the clinical thresholds averaged less than 0.1 dB. This exact agreement is clearly a coincidence as the distribution of differences is bimodal with peaks at approximately −9 dB and +5 dB (see Fig. 4). Furthermore the arithmetical average of the errors of the individual estimates, frequency by frequency, was nearly 10 dB. In two cases our average estimate for a child, at all five frequencies, was 18 dB or more in error (see Fig. 4) but we nevertheless believe that the method has great potentialities for the assessment of the hearing of very young deaf children.

ACKNOWLEDGEMENTS

In 1958 Dr. Atze Spoor explored, in our laboratory, several parameters of the evoked response (unpublished). He used a method of photographic superposition to obtain average responses. Our present digital data processing computer was designed and constructed by A. Maynard Engebretson and Donald Glaeser under the direction of Dr. Jerome R. Cox, Jr. (Engebretson, Cox & Glaeser 1964). Mrs. Shirley K. Hirsh and Mrs. Joyce Shelnutt assisted in obtaining the ER audiograms of the children.

RÉSUMÉ

On ne peut incorporer la réaction corticale lente provoquée en un schéma plausible du fonctionnement de l'information auditive, à cause de sa longue durée, sa variabilité, sa structure complexe, sa curieuse distribution anatomique et ses relations semi-spécifiques à travers les modalités sensorielles. Nous espérons que les réactions provoquées donneront quelque information audiométrique et peut-être neurologique d'une vraie valeur clinique, mais ceci doit être établi sur une base purement empirique.

ZUSAMMENFASSUNG

Elektrische Antworten auf akustische Reize können vom Scheitel des Menschen abgeleitet und mit Elektronenrechnern ermittelt werden. Eine Art dieser Antworten hat eine beträchtliche Latenz und besitzt einen langsamen Zeitgang. Sie verspricht klinischen Wert für die Erfassung des peripheren und vielleicht auch gewisser Teile des zentralen Hörorgans in ihrer Funktion. Die Notwendigkeit des Schlafes oder der Sedierung entfällt, desgleichen ist keinerlei Schulung oder Mithilfe des Patienten erforderlich, lediglich ein Ruhigsitzen für jeweils 1–2 Minuten. Der lange Zeitgang und die langsame Rückbildung der langsamen Rindenantwort, ihre Vielfalt und komplexe Form, ihre eigentümliche anatomische Verteilung und ihre halbspezifischen Beziehungen zu anderen Sinnesmodalitäten lassen bisher keine Einordnung in irgendein einleuchtendes Schema der Ge

was almost the same for both groups of experiments. The animals were anesthetized by intraperitoneal injections of Dial (60 mgs/kgm body weight). The posterior fossa was opened by a dorsal approach and the cerebellum either retracted or partially aspirated to expose the auditory nerve cochlear nucleus region. The microelectrodes were positioned with the aid of an operating microscope. During recording, the preparation was alone in the soundproof, electrically shielded and vibration isolated chamber, the electrode being advanced by a hydraulic remote-control manipulator.

Acoustic stimuli were delivered by a Bruel and Kjaer 1" condenser microphone that was used as an earphone and positioned near the tympanic membrane in a closed system. Stimulus levels are given in terms of voltage into the earphones. The reference levels were 100 V for clicks, and 200 V p-p for tonal signals. A gross electrode placed near the round window permitted the recording of cochlear potentials. The thresholds of round window neural responses were generally −80 db for clicks.

The electrical activity registered by the microelectrode and the round window gross electrode was recorded on magnetic tape and later processed on the TX-0 computer at the Massachusetts Institute of Technology. The techniques have been described in detail previously (Gerstein & Kiang 1960). It is sufficient here to recall that a PST histogram plots the distribution of the times at which events occur following stimulus presentation. In the present context the events are spike discharges recorded by microelectrodes. The PST histograms are particularly useful in studying the response patterns of these spikes.

Threshold data were obtained by visual inspection of spike trains during the experiment. Bursts of tone 50 msec in duration, were presented at a rate of 10 bursts/second. At each selected stimulus level the frequency content of the tone bursts was systematically changed and the frequencies at which spikes became synchronized with the tone bursts were noted. The extreme frequencies at which responses occur can be plotted as functions of stimulus level to give tuning curves. The point of maximum sensitivity on this curve is the characteristic frequency CF.

Since the purpose of this paper is to compare responses from two locations, the data had to be collected under comparable conditions. Except for the recording microelectrodes and minor differences in surgical exposure the experimental conditions were virtually identical. The two types of microelectrodes were:

1. Hyperfine pipettes with tip diameters in tenths of microns. The pipettes are filled with a 3 M KCl solution (Tasaki, Polley & Orrego 1954).
2. Indium filled pipettes with a large (> 5 μ) ball of platinum plated on the tip (Gestel and Howland, Lettvin & Pitts 1959).

The relative sizes of the electrodes, the fibers, and some of the cells are shown in Fig. 1.

STIMULUS CODING IN THE AUDITORY NERVE AND COCHLEAR NUCLEUS[1]

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The average time pattern of response of any auditory nerve fiber to simple acoustic stimuli is predictable from its tuning curve and rate of spontaneous discharge. In contrast, units in the cochlear nucleus may exhibit radically different response patterns to the same stimulus though their tuning curves and rates of spontaneous discharge are virtually identical. Messages carried by the auditory nerve are apparently recoded in the cochlear nucleus in a number of different ways. Consequently, the nucleus should not be considered merely as a relay station.

INTRODUCTION

In normal mammalian hearing, mechanical events in the inner ear give rise to discharges in the fibers of the auditory nerve. Each auditory nerve fiber enters the cochlear nucleus and branches to innervate many cells (Ramon y Cajal, 1952; Lorente de No, 1933). The synaptic connections in this nucleus offer the first opportunity for extensive recoding of information carried by the auditory nerve fibers. It is therefore of prime interest to compare the activity of fibers in the auditory nerve with that of cells in the cochlear nucleus. The present report is a brief summary of efforts to compare certain selected features of electric responses recorded from units in both nerve and nucleus. Emphasis has been placed on response patterns to simple acoustic stimuli. No attempt has been made to describe the gross electric potentials that parallel the unit potentials.

METHODS

The data to be presented have been obtained from approximately 100 adult cats. In half of these experiments the auditory nerve was studied; in the other half the cochlear nucleus was studied. The surgical preparation

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was almost the same for both groups of experiments. The animals were anesthetized by intraperitoneal injections of Dial (60 mgs/kgm body weight). The posterior fossa was opened by a dorsal approach and the cerebellum either retracted or partially aspirated to expose the auditory nerve-cochlear nucleus region. The microelectrodes were positioned with the aid of an operating microscope. During recording, the preparation was alone in the 'soundproof', electrically shielded and vibration-isolated chamber, the electrode being advanced by a hydraulic remote control manipulator.

Acoustic stimuli were delivered by a Bruel and Kjaer 1" condenser microphone that was used as an earphone and positioned near the tympanic membrane in a closed system. Stimulus levels are given in terms of voltage into the earphones. The reference levels were 100 V for clicks, and 200 V p-p for tonal signals. A gross electrode placed near the round window permitted the recording of cochlear potentials. The thresholds of round window neural responses were generally −80 db for clicks.

The electrical activity registered by the microelectrode and the round window gross electrode was recorded on magnetic tape and later processed on the TX-0 computer at the Massachusetts Institute of Technology. The techniques have been described in detail previously (Gerstein & Kiang 1960). It is sufficient here to recall that a PST histogram plots the distribution of the times at which events occur following stimulus presentation. In the present context the events are spike discharges recorded by microelectrodes. The PST histograms are particularly useful in studying the response patterns of these spikes.

Threshold data were obtained by visual inspection of spike trains during the experiment. Bursts of tone 50 msec in duration, were presented at a rate of 10 bursts/second. At each selected stimulus level the frequency content of the tone bursts was systematically changed and the frequencies at which spikes became synchronized with the tone bursts were noted. The extreme frequencies at which responses occur can be plotted as functions of stimulus level to give tuning curves. The point of maximum sensitivity on this curve is the characteristic frequency, CF.

Since the purpose of this paper is to compare responses from two locations, the data had to be collected under comparable conditions. Except for the recording microelectrodes and minor differences in surgical exposure the experimental conditions were virtually identical. The two types of microelectrodes were:

1. Hyperfine pipettes with tip diameters in tenths of microns. The pipettes are filled with a 3 M KCl solution (Tasaki, Polley & Orrego, 1954).
2. Indium filled pipettes with a large (>5 μ) ball of platinum plated on the tip (Gesteland, Howland, Lettvin & Pitts 1959).

The relative sizes of the electrodes, the fibers and some of the cells are shown in Fig. 1.

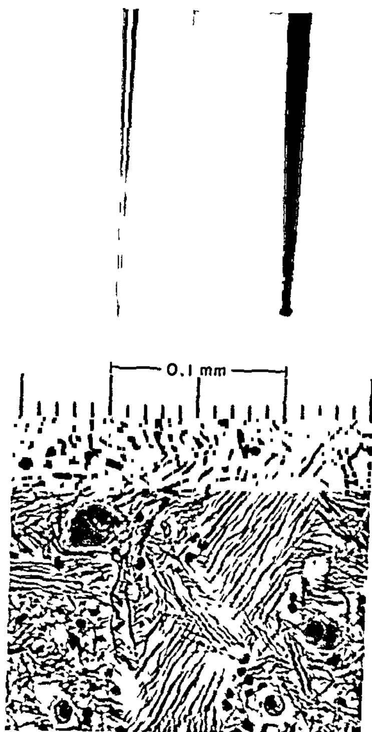


Fig. 1 Photomicrograph of the two types of electrodes discussed in this paper with a photomicrograph of a small part of the cochlear nucleus The electrode on the left is the 3 M KCl filled pipette The electrode on the right is the indium filled pipette with a platinum ball plated on the tip The large cells in the picture below are in the interstitial part of the cochlear nucleus The fibers coursing from the bottom left to the upper right of the picture are the auditory nerve fibers

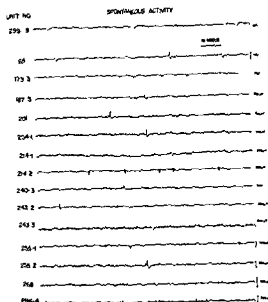


Fig. 2. *Sample spike trains of spontaneous activity for a number of units.* The spikes for Unit 219 19 were obtained by using a KCl filled pipette inserted into the auditory nerve. *The spikes in other traces* were obtained by using metal filled electrodes inserted into *various regions in the cochlear nucleus.* Upward *deflection* represents negativity at the electrode relative to the headholder.

RESULTS

The use *of two types* of microelectrodes was made necessary by the fact *that* activity from auditory nerve fibers and cochlear nucleus units must be *clearly differentiated* in order to compare their responses. When the *fluid filled* micropipettes are inserted into that *portion of* the auditory nerve which contains no cell bodies of *neurons, spike discharges* are recorded only with waveforms that *are illustrated by* the spikes in the top trace *of Fig. 2.* These discharges have been studied in detail previously and may be *presumed to be* characteristic of auditory nerve fibers (*Kiang, Watanabe,* Thomas & Clark, 1962). The fluid filled type of electrode is not so useful for recording in the *cochlear nucleus,* since not only cell bodies but also auditory nerve *fibers, higher* order fibers, and efferent fibers are present in the *nucleus. The* metal electrode with a large platinum ball plated on the tip is *more selective.* In the nucleus this metal microelectrode records a variety *of* spike waveforms, *some of* which are shown in Fig. 2. When these particular metal microelectrodes *are inserted* into the auditory nerve, no spike discharges can *be seen. If one* accepts that the large tip is incapable of recording auditory nerve *fiber* activity, then the spikes obtained by the use of the metal microelectrodes must represent the activity of *cells,* or of parts of cells that are of higher order. It is *possible that only elements* with large extracellular electrical fields *can* be recorded with these elec-

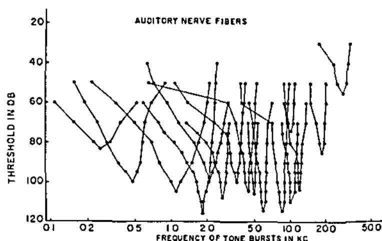


FIG. 3. Sample tuning curves for 16 auditory nerve fibers. The acoustic stimuli were tone bursts with 2.5 msec rise-fall times and 50 msec durations presented at 10/sec.

trodes. Several observations support this possibility. (1) The distance along an electrode track over which the activity of a given unit may be recorded is usually hundreds of microns (μ), whereas auditory nerve fibers can be held in electrical "contact" with fluid-filled electrodes over only a few microns. (2) The relative number of active units per electrode track is far less with metal electrodes than with fluid-filled electrodes, even when the two types of electrodes are inserted into the same general region. (3) Sustained injury discharges of units are frequently obtained with both fluid-filled and metal electrodes in the cochlear nucleus. Such discharges are never found in recordings from the auditory nerve fibers. Thus injury discharges are characteristic of elements that are not present in the nerve. This observation, of course, does not mean that the metal electrodes record *only* from cell bodies. (4) The metal electrodes record spike discharges, even during withdrawal of the electrode, whereas the fluid-filled electrodes do not. In practice the metal electrodes are first inserted a given distance into the nucleus, and data are recorded only at points reached during the with-

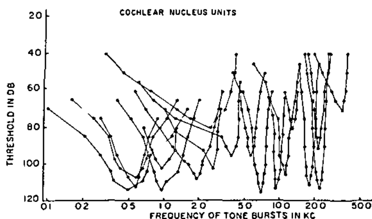


FIG. 4. Sample tuning curves for 18 cochlear nucleus units. The stimulus conditions are the same as in Fig. 3.

drawal of the electrode This practice virtually eliminates the presence of injury discharges during the recording of data

The preceding considerations afford a working hypothesis that spike activity recorded in the cochlear nucleus by the metal microelectrodes represents activity of units of higher order than the so-called primary units the auditory nerve fibers

A *Tuning curves*

One of the most commonly studied characteristics of auditory units is the tuning curve connecting points obtained in a threshold *vs* frequency plot for response to tonal stimuli Figure 3 shows such tuning curves for auditory nerve fibers and Fig 4 shows curves for cochlear nucleus units The general shapes of the curves in the two figures appear to be comparable The curves for cochlear nucleus units certainly cannot be said to be more narrow than those for auditory nerve fibers If anything they are slightly broader There are great variations in the threshold of both sets of units at any given CF, which cannot be accounted for by inadequate control of stimulus levels

The selective frequency sensitivity of individual units in both nerve and nucleus implies a selective projection of auditory nerve fibers to cochlear nucleus units *In the strictest sense therefore it may be valid in comparing* auditory nerve fibers and cochlear nucleus units only to compare the activities of units with the same CF

B *Patterns of responses to clicks*

The click responses of auditory nerve fibers with low CF generate multiple peaks in the PST histogram with the interpeak interval equal to 1/CF (Kiang Watanabe Thomas & Clark 1962) The click *responses of cochlear* nucleus units with low CF almost always show only a single peak in the PST *histogram If the units represented in Fig 5 are* directly or indirectly connected as is implied by their identical CF the activity *in the cochlear* nucleus unit cannot be a simple relaying of discharges from auditory nerve fibers

Since clicks are relatively punctate in time they are useful in making comparative measurements of response latencies In Fig 5 the first peak in the histogram for the auditory nerve fiber occurs at 2 45 msec while the peak in the histogram for the cochlear nucleus *unit occurs at 3.55 msec* In a previous study it was shown that all auditory nerve fibers with CF above 2.5 kc have nearly the same latencies in response to clicks (Kiang Watanabe Thomas & Clark 1962) Elements with CF above 4 kc were *therefore studied* with clicks at a moderate level (−50 db) The distribution of latencies for a number of auditory *nerve fibers and* cochlear nucleus units is plotted in Fig 6 There is very little overlap between the distribution of the two elements

Not only are response latencies different for auditory nerve fibers and

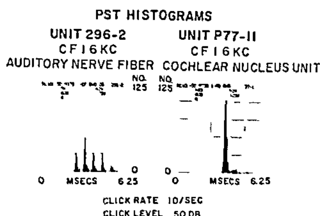


Fig. 5 Patterns of click responses from an auditory nerve fiber and a cochlear nucleus unit, both with CF at 1.6 kc. Each histogram consists of 125 vertical bars. Zero time is the instant at which the electric pulse is delivered to the earphone. The ordinates represent numbers of spikes, the abscissas represent time after zero time. One minute of data was processed for each histogram.

cochlear nucleus units but the way latencies change with click rate is different. Figure 7 shows that as click rate increases from 10 clicks/sec to 200 clicks/sec, the latency of the first peak in the histogram for the auditory nerve fiber increases by 0.1 msec; the latency of the peak in the histogram for the cochlear nucleus unit increases by 0.3 msec.

Perhaps even more striking than the latency shifts is the sharpness of the peak in the histogram for the cochlear nucleus unit at the low click rates. It is a common finding that the histograms of cochlear nucleus activity show narrower peaks than are found in histograms of auditory nerve fiber activity, even when the same stimulus is used. The situation for elements

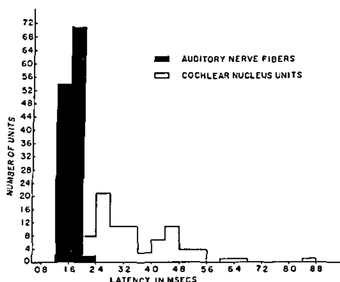


Fig. 6 Histogram of response latencies for 127 units from the auditory nerve and 53 units from the cochlear nucleus. The CF of these units have been selected to be 4 kc or higher. The stimulus was 10/sec delivered at a level of −50 db re 100 V p-p into the earphone.

Fig 7

Fig 9

Fig 7 Response patterns of an auditory nerve fiber and a cochlear nucleus unit, both of low CF, to clicks presented at *five different rates* One minute of data was processed for each histogram

Fig 9 Response patterns of an auditory nerve fibre and a cochlear nucleus unit, both of low CF to clicks presented at several stimulus levels One minute of data was processed for each histogram

with high CF is shown in *Fig 8* The peak of the PST histogram for the responses of the auditory *nerve fiber* does not *shift in* time as the click rate is increased from 10/sec to 100/sec *The three* cochlear nucleus units show different degrees of latency shifts *Unit 14-5* shows no increase in latency, while Unit 15-1 shows an increase *of 0 75* msec and Unit 21-5 an increase of 1 1 msec

Figures 9 and 10 *compare* the response patterns of an auditory nerve

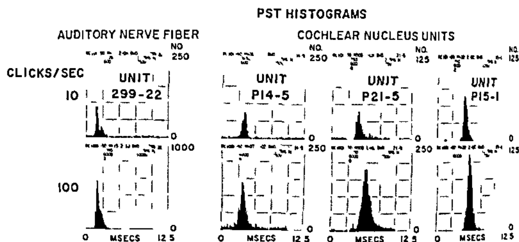


FIG 8 Response patterns of an auditory nerve fiber and two, three cochlear nucleus units, all of high CF, to clicks Histograms as shown for two rates of clicks Click levels for the units from left to right −50 db, −40 db, −70 db, and −60 db Forty eight seconds of data were processed for the 100/sec histogram of Unit P14-5 One minute of data was processed for the other histograms.

fiber and those of a cochlear nucleus unit as click level is changed Both units in Fig 9 have low CF. Here the individual peaks in the histogram for the fiber do not show time shifts in the histogram, the largest peak remaining at 1 8 msec. The latency of the peak for the cochlear nucleus unit shifts, however, *from 1 1 msec to 2 5 msec. Since* these two units have somewhat different thresholds and CF, comparison between them may not be entirely valid. They are used to illustrate the general finding that cochlear nucleus units usually show greater decreases in latency with changes in stimulus level than do auditory nerve fibers (Kiang, Goldstein & Peake, 1962) Furthermore, these decreases in latency are greatest at low stimulus levels where the auditory nerve fibers are most constant in latency with respect to changes in stimulus level However, auditory nerve fibers with high CF *do* exhibit decreases in response latency with increasing stimulus level, examples can be found in which the shifts for fibers are as great as the shifts for cochlear nucleus units For instance the peak for Unit 309-32 in Fig 10 shifts by 0 5 msec, while the corresponding peak for unit P77-7 shifts by 0 6 msec Note that at the higher stimulus levels multiple peaks *in the PST histograms appear for cochlear nucleus units* The time interval between these peaks bears no obvious relation to the CF of the units

The foregoing data indicate that there is no one-to-one correspondence of time pattern in the responses of auditory nerve fibers and cochlear nucleus units to identical stimuli and to changes in stimuli This suggestion is supported by the following results of experiments with bursts of tone

C *Patterns of response to bursts of tones at CF*

Auditory nerve fibers respond to short tone bursts at or near the CF, with a brief transient increase in discharge rate followed by a decline to a

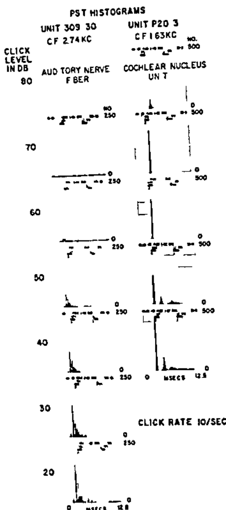


Fig 10

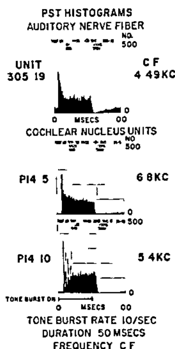


Fig 11

Fig. 10 Response patterns of an auditory nerve fiber and a cochlear nucleus unit both of high CF to clicks presented at several stimulus levels One minute of data was processed for each histogram

Fig. 11 Response patterns of an auditory nerve fiber and two cochlear nucleus units to short 50 msec bursts of tone *The level of tone was – 0 db for Unit 305 19 and* 50 db for Unit P14 5 and 55 db for Unit P14 10 One minute of data was processed for each histogram

steady level that is still above the level of spontaneous discharge (Fig 11) While some cochlear nucleus units may also exhibit this pattern of response others do not For example Unit P14 5 in Fig 11 has a response pattern that resembles that of auditory nerve fibers Unit P14 10 has a response pattern that is characterized by a number of distinct peaks in the PST histogram which are synchronous with the onset of the tone burst The successive peaks become smaller until a steady level of activity is reached The intervals between peaks are unrelated to the CF of such units

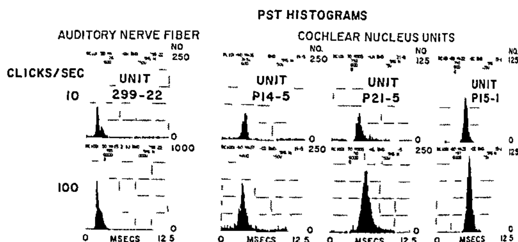


FIG 8 Response patterns of an auditory nerve fiber and two, three cochlear nucleus units, all of high CF, to clicks Histograms as shown for two rates of clicks Click levels for the units from left to right −50 db, −40 db, −70 db, and −60 db Forty eight seconds of data were processed for the 100/sec histogram of Unit P14 5 One minute of data was processed for the other histograms

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C *Patterns of response to bursts of tones at CF*

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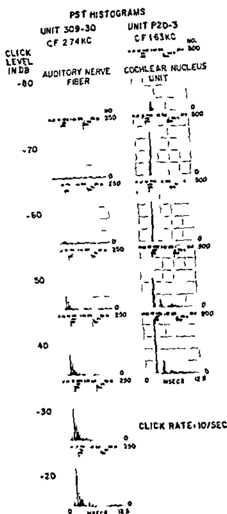


Fig 10

PST HISTOGRAMS
AUDITORY NERVE FIBER
UNIT 305-19 C.F. 4 49KC
0 MSECS 100
COCHLEAR NUCLEUS UNITS
P14-5 6 8KC
P14-10 5 4KC
TONE BURST ON
0 MSECS 100
TONE BURST RATE 10/SEC
DURATION 50 MSECS
FREQUENCY C F

Fig 11.

Fig 10 Response patterns of an auditory nerve fiber and a cochlear nucleus unit, both of high CF, to clicks presented at several stimulus levels One minute of data was processed for each histogram

Fig 11 Response patterns of an auditory nerve fiber and two cochlear nucleus units to short (50 msec) bursts of tone The level of tone was −70 db for Unit 305-19, and −50 db for Unit P14 5, and −55 db for Unit P14-10 One minute of data was processed for each histogram

steady level that is still above the level of spontaneous discharge (Fig 11). While some cochlear nucleus units may also exhibit this pattern of response, others do not For example, Unit P14-5 in Fig. 11 has a response pattern that resembles that of auditory nerve fibers. Unit P14-10 has a response pattern that is characterized by a number of distinct peaks in the PST histogram which are synchronous with the onset of the tone burst. The successive peaks become smaller until a steady level of activity is reached. The intervals between peaks are unrelated to the CF of such units.

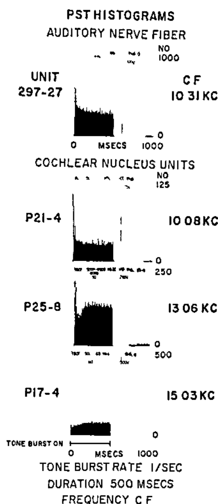


Fig 12

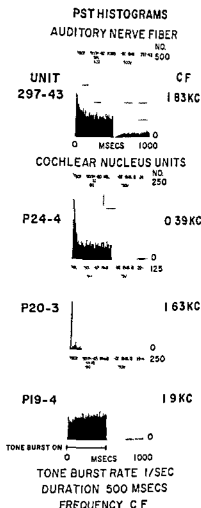


Fig 13

Fig 12 Response patterns of an auditory nerve fiber and three cochlear nucleus units all of high CF to long (500 msec) bursts of tone The level of tone was −70 db for Unit 297 27 −90 db for Unit P21 4 −85 db for Unit P25 8 and −65 db for Unit P17 4 Two minutes of data were processed for the histogram of Unit 297 27 One minute of data was processed for the histograms of Units P21 4 and P17 4 two and a half minutes of data were processed for the histogram of Unit P25 8

Fig 13 Response patterns of an auditory nerve fiber and three cochlear nucleus units all of low CF to long (500 msec) bursts of tone The level of tone was −60 db for Units 297 43 and P24 4 and −65 db for Units P20 3 and P19 4 Two minutes of data were processed for the histogram of Unit 297 43 One minute of data was processed for the other histograms

Figures 12 and 13 illustrate response patterns to long tone bursts Since the durations of the bursts are ten times longer than those for Fig 11, the finer details of the transient peaks cannot be seen In Fig 12, the response pattern of Unit P21-4 resembles that of the auditory nerve fiber (297-27) in having a brief transient peak followed by a decline to a steady level The activity of Unit P25-8, however, not only shows a transient increase but also exhibits a later longer-lasting (100–200 msec) dip in the PST histogram, and finally reaches a steady level Unit P17-4 has a gradually increas-

ing rate of discharge as long as the tone burst is on; after several hundred milliseconds, a steady level of activity is reached. In Fig 13 the histogram for Unit P24-4 resembles that of the auditory nerve fiber (297–43). The histogram for Unit P19-4 resembles to some degree the histograms for both Units P17-4 and P25-8 in Fig. 12. The histogram for P20-3 shows a transient increase in the discharge rate that rapidly falls to a low level, eventually ceasing to discharge—even if the stimulus is still on Units such as P20-3 do not show spontaneous discharges and do not respond to continuous stimulation. No units were ever found to respond at the "off" of tone bursts, whether the bursts were short or long (Sandel & Kiang, 1961; Kiang & Sandel, 1961).

The use of long tone bursts seems to reveal differences in response behavior that are not so obvious under click stimulation. The proper choice of stimulus conditions is apparently highly important in differentiating different "types" of units. Preliminary findings indicate that the differences in response patterns to long tones are not correlated with differences in CF, but rather to anatomical location of units within the various subdivisions of the cochlear nucleus.

Complex phenomena that may involve inhibitory mechanisms appear when combinations of simple stimuli are used, but these phenomena have not been explored sufficiently to justify inclusion in this report.

DISCUSSION

Although there are many gaps in the existing descriptions of auditory nerve fiber activity, results from anesthetized cats indicate that the time patterns of response to simple stimuli such as clicks and tone bursts can be studied quantitatively (Kiang, Watanabe, Thomas & Clark, 1962). As a first approximation, the response patterns to simple stimuli seem to be closely related to CF. If the CF of an auditory nerve fiber is known, it is possible to predict the general features of the response patterns that will appear in the PST histograms. This does not seem possible for units in the cochlear nucleus. Knowledge of the CF alone is insufficient to describe even the grossest aspects of the time pattern of response to tone bursts In fact, the very concept of CF has to be restricted to tone bursts, since many units do not respond to continuous tones The increased variety of response patterns in the nucleus as compared with the nerve is consistent with earlier observations that the time pattern of spontaneous activity for units in the cochlear nucleus is more varied and complex than that found for the auditory nerve fibers (Rodieck, Kiang & Gerstein, 1962, Kiang, 1963)

At present, the greatest uncertainty in this study lies in the presumption that the electrodes gave a reasonably "fair" account of events at the microscopic level The present understanding of how various specific types of electrodes might influence recordings remains at a primitive level of specula-

tion. Even the fluid-filled micropipettes may systematically have missed certain fiber components in the nerve. The metal microelectrodes presumably record extracellular electric fields of cell bodies and dendrites, but there are no satisfactory generalizations to permit estimation of the biases introduced by these electrodes. Can they record activity of fibers if they are near either nodes or endings? Do they emphasize cells with large dendritic trees? Are certain types of cells systematically missed? These questions cannot be answered at the present time. Those units in the cochlear nucleus that closely resemble the auditory nerve fiber in response behavior may be nodes, or endings of auditory nerve fibers. The only evidence against such a suggestion is that the activity of such units seems to be recordable over long distances along an electrode track. It may well be that just as a variety of stains is necessary to demonstrate the microanatomical relations in this region, a variety of electrodes, each with its own bias, may be necessary to explore all aspects of the electrical activity.

Whatever the interpretations of the anatomical correlates of the electrophysiological units, the limitations reflect more upon the completeness than on the validity of recorded data. Even from the cursory summary provided by the present report, a number of conclusions are possible.

1. The similarity of tuning curves from auditory nerve fibers and cochlear nucleus units offers no support for notions of increasing sharpness of tuning at successively higher levels of the auditory nervous system (Tasaki, 1954; Whitfield, 1957; Katsuki, 1961). It does demonstrate an orderly projection of the auditory nerve fibers onto cochlear nucleus cells, confirming both earlier electrophysiological observations (Rose, Galambos & Hughes, 1959; Rose, 1960), and anatomical findings (Ramon y Cajal, 1952; Lorente de No, 1933 a).

2. There are latency differences in responses from units recorded from the two locations, confirming an earlier suggestion by Tasaki & Davis (1955) based on recordings from guinea pigs. This difference may include conduction time along the fiber that enters the cochlear nucleus, the synaptic delay at the active unit, and the possibility of intercalated neurons. The broad distribution of latencies for cochlear nucleus units suggests that many of these units may not be directly connected with auditory nerve fibers. Reference to all units in the cochlear nucleus as being second order is clearly inadequate.

3. The differences in response patterns of auditory nerve fibers and cochlear nucleus units, even to such simple stimuli as clicks and bursts of tone, suggest that the detailed features of the time patterns are not necessarily preserved in higher order units, and that extensive recoding exists at the level of the cochlear nucleus. The differences in response patterns of various cochlear nucleus units suggest that such recoding takes place in a variety of ways. This possibility is not surprising, since the auditory system, in performing its many functions, must selectively focus on different aspects

of the acoustic signals for different tasks. Thus the cues necessary for sound localization may be quite different from those necessary to make frequency discriminations, the cues *sufficient to alert* or awaken the organism may not suffice for the understanding of speech, the affective qualities of acoustic stimuli may be based on *different aspects of stimulus characteristics than those necessary for loudness judgments*.

The experimental results offer opportunities to introduce a number of classical physiological concepts as explanatory mechanisms. Thus the large changes in latency with stimulus level for units in the cochlear nucleus suggest convergence of auditory nerve fibers on these units. Convergence also would be suggested if the tuning curves for cochlear nucleus units were in fact slightly broader than those of auditory nerve fibers. Inhibitory mechanisms can be conveniently invoked to explain the lack of multiple peaks in the click PST histogram of cochlear nucleus units with low CF. Inhibitory mechanisms may also be important in the case of units that respond only to transient stimuli. Mechanisms underlying adaptation undoubtedly become more important as the stimuli become more prolonged. In short, there is no lack of possible physiological explanations for the present data.

The more immediate need is for systematic studies of how response *patterns change with changes in stimulus parameters* and how these patterns are correlated with location in the cochlear nucleus. There is no *typical cochlear nucleus unit (Moushegian, Rupert & Galambos, 1962)*. Instead there are many different "types" of units that have radically *distinct profiles of behavior with respect to acoustic stimuli*. Thus it is probably not valid to generalize the findings from any one unit to units that belong to another "type". Even without the introduction of contralateral stimulation (Pfalz, 1962) and other possible effects of efferent pathways (Rasmussen, 1960) the notion that the cochlear nucleus is a simple relay nucleus, or even that it performs a single transformation on the incoming afferent inputs, is difficult to justify in view of existing evidence.

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The author wishes to acknowledge the contributions of Dr. T. Watanabe, Dr. R. R. Pfeiffer, Louise F. Clark, Eleanor C. Thomas, Marjorie F. Saunders and Ann S. N. Backus, all of whom participated in many of these experiments. It is a pleasure to thank Professor W. A. Rosenblith for his support and encouragement of these efforts.

RÉSUMÉ

Étant donné le domaine de réponse aux sons purs et le *nombre des potentiels d'action* émis spontanément par seconde *par une fibre du nerf auditif*, on peut en déduire la manière dont la *fibre répondra* en moyenne à toute la *gamme des*

stimuli sonores simples. Dans le noyau cochléaire on observe des phénomènes nettement différents, deux unités peuvent avoir des domaines de réponse et des nombres de décharges spontanées identiques et néanmoins avoir des patterns caractéristiques radicalement différents en réponse à des stimuli déterminés. Les messages du nerf auditif sont apparemment recodés dans le noyau cochléaire de façons variées. Ainsi le noyau ne peut pas être considéré comme un noyau de relais fin et simple.

ZUSAMMENFASSUNG

Der durchschnittliche zeitliche Verlauf der Reaktion einer Hörnervenfaser auf einfache akustische Reize kann aus dessen Abstimmkurve („tuning curve") und der Häufigkeit spontaner Entladungen vorausgesagt werden. Die Elemente des Cochlearis-Kernes können dagegen grundsätzlich unterschiedliche Reaktionsverläufe bei demselben Reiz aufweisen, obwohl deren Abstimmkurven und Häufigkeiten der spontanen Entladungen prinzipiell identisch sind. Augenscheinlich werden die über den Hörnerv übertragenen Nachrichten im Cochlearis-Kern auf verschiedene Weise umkodiert. Infolgedessen sollte der Kern nicht ausschliesslich als Relaisstation betrachtet werden.

REFERENCES

Galambos, R. and Hughes, J. R. 1959. *Bull. Johns Hopkins Hosp.* *104*, 211.
Gerstein, G. L. and Kiang, N. Y. S. 1960. *Biophys. J.* *1*, 15.
Gesteland, R. C., Howland, B., Lettvin, J. Y. and Pitts, W. H. 1959. *Proc. IRE* 47, 1856.
Katsuki, Y. 1961. In *Sensory Communication* (ed. W. A. Rosenblith) p. 561. The M.I.T. Press, Cambridge, Mass., and John Wiley and Sons Inc., New York.
Kiang, N. Y. S. 1963. *J. Acoust. Soc. Amer.* 35, 793 (A).
Kiang, N. Y. S., Goldstein, M. H. Jr., and Peake, W. T., 1962. *IRE Trans. on Information Theory* Vol. IT-8, p. 113.
Kiang, N. Y. S., Watanabe, T., Thomas, E. C., and Clark, L. F. 1962. *Ann. Otol.* 71, 1009.
Kiang, N. Y. S. and Sandel, T. T. 1961. *Arch. Ital. Biol. (Pisa)* 99, 121.
Lorente de Nó, R., 1933 (*a*) *Laryngoscope* 43, 1.
— 1933 (*b*) *Laryngoscope* 43, 327.
Moushegian, G., Rupert, A. and Galambos, R. 1962. *J. Neurophysiol.* 25, 515.
Pfalz, R. K. J., 1962. *J. Acoust. Soc. Amer.* 34, 1472.
Ramón y Cajal, S., 1952. Histologie du système nerveux de l'homme et des vertébrés I, 1909. Madrid Institute Ramón y Cajal (French edition).
Rasmussen, G. L. 1960. In *Neural Mechanism of the Auditory and Vestibular Systems* (eds. G. L. Rasmussen and W. F. Windle) Charles Thomas, Springfield, Ill., U.S.A.
Rose, J. E. 1960. In *Neural Mechanisms of the Auditory and Vestibular Systems* (eds. G. L. Rasmussen and W. F. Windle) Charles Thomas, Springfield, Ill., U.S.A.
Sandel, T. T. and Kiang, N. Y. S., 1961. *Arch. Ital. Biol. (Pisa)* 99, 105.
Rodieck, R. W., Kiang, N. Y. S. and Gerstein, G. L. 1962. *Biophys. J.* 2, 351.
Tasaki, I. 1954. *J. Neurophysiol.* 17, 97.
Tasaki, I. and Davis, H. 1955. *J. Neurophysiol.* 18, 151.
Tasaki, I., Polley, E. H. and Orrego, F. 1954. *J. Neurophysiol.* 17, 454.
Whitfield, I. C. 1957. In *Progress in Biophysics and Biophysical Chemistry* 8, 247.

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AUDIOMETRIC ASPECTS AND MULTISENSORY POWER FUNCTIONS OF ELECTRONICALLY AVERAGED SLOW EVOKED CORTICAL RESPONSES IN MAN

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Erlangen, Germany

Aus dem Physiologischen Institut der Universität Erlangen-Nürnberg

Based upon some experimental work during the last two years we were able to demonstrate that it is possible to record extracranially a characteristic slowly evoked cortical response of a rather complex nature time locked to auditory stimuli. All potentials are evoked by sinusoidal tones of 1 second duration. They were averaged by means of a special type of physiological computer. It was possible to record clearly intensity related human cortical responses of medium latency (second negative deflection, latency 150 to 180 msec). Thus a quantitatively reliable correlation with the stimulus parameters was obtained.

The late second negative deflection was measured and the results were compared with those of the Stevens group. This part of our cortical responses when plotted double logarithmically versus intensity clearly showed the identical exponents of Stevens' power functions when stimulating the auditory and the somesthetic system, the latter especially by both vibratory and electric pain eliciting qualities. This correlation between electrophysiological and psychophysical sets of data clearly shows the same correspondent steepness of intensity functions for different qualities and modalities of stimuli.

It is an old dream of physiologists to be able to compare quantitatively the data which one can obtain by two methodologically completely different techniques of getting responses of a human subject (or animal). Using psychophysical explorations in man it is possible to measure threshold curves as well as data of the type of magnitude scales like those explored during the last decade especially by S. S. Stevens and his group. This certainly is the classical technique of "subjective" audiometry. One of the slightest presuppositions for this type of experiments is that the subject is awake, is able to respond to any type of motor reaction which involves a certain normal level of consciousness and that he is also mentally in a classical and not in a pathological state thus enabling logical responses. He must also be able to use the usual means of communications, as well as e.g. language which may not be the case in children and babies or in analphabets. He certainly therefore must also be able to understand the experimental situation. He therefore could not go to sleep or be anaesthetized

For all those reasons the second, completely different technique, the so called "objective" one, was used by physiologists especially in animals which can respond only to a certain degree after a long behavioural training in a cooperative and reliable manner with the physiologist performing the experiment. *By using electrophysiological methods, measuring* some sort of potentials recorded from any place within the sensory channel either watching single units by means of the use of superfine microelectrodes or groups of receptor or nerve cells or nervefibers by means of insertion of macro electrodes, it is possible to gain sets of data which may or may not correspond to those data obtained "subjectively" in man, at least in the basic trends and principles of the functional relationships in a numerical sense.

Now, whilst those comparisons in animals led to fairly well comparable results, the trail to be able to make "objective" audiometry in man, "objective" defined in the sense stated above, and even to compare the objective and subjective data in man, remained up to a few years ago not more than a dream and a vague idea until physiologists got this fine new tool in their hands, namely the modern physiological computer. The reason why it was not possible to obtain sufficient information from the only technique which can be used without surgery in man, the EEG, is that the stimulus looked responses within the EEG are hidden by the tremendously larger deflections of the spontaneous activity. The solution was the use of electronic averages and autocorrelators, which were introduced by some pioneering groups of engineers at MIT, e.g. the group of Walter Rosenblith and others. Those averages are being built in a few places in the world, e.g. by Cox at the group of Dr. Davis (St. Louis) and besides others also at our laboratory (*Keidel, 1959, Keidel & Spreng, 1963*). We were *able to report about* the complex, strictly stimulus-looked type of responses to acoustical stimuli in man at Athens two years ago at the last meeting of ORLAS.

As we then described, the "objective" response to a sinusoidal tone of 1 second duration, delivered at a frequency of 1 kc to both ears of an awake subject sitting inside an anechoic chamber, consists of an intraindividually rather constant and—for a given state—invariant form. Recording from the glabella (or vertex) versus temporal bone (or any other location at the skull), a first quick response, having a latency of about 30 msec, can be separated from a second one, in the mean about 60 msec, after onset of stimulus and after that a third—in respect to the two first ones—late response a large inverse deflection somewhere between 90 and 200 msec with a mean value around 150 to 160 msec. The whole complex is followed by highly variable, long-lasting peaks of the same polarity as the first two quick ones, 300 to 900 msec after stimulus onset (Fig. 1).

We now stick only to the late response that shows a latency of 150 msec which is surface-positive at the temporal bone and surface-negative at the glabella precisely as described in our preceding paper of Athens (Keidel & Spreng, 1963). This deflection only can be used according to our experience for "objective" audiometry in man.

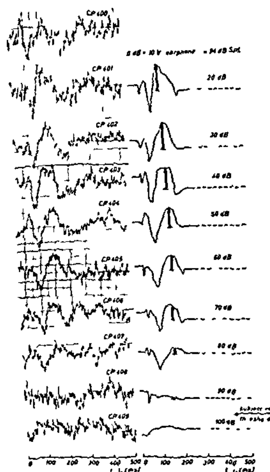


FIG. 1 Series of slow evoked potentials from the human skull to various auditory stimulus intensities. To reveal stimulus response relationships only the late response was counted which is indicated by a thick arrow in each scheme of the right row

The reason for that is, as N. Y. S. Kiang and especially Bickford showed so clearly during the last years, that the two first quick peaks are generalized muscle reactions elicited by the auditory stimuli in a way comparable with the lid reflex which is also of muscular origin and only triggered by the light stimulus. We in our laboratory repeated the Bickford experiments and were able to record this activity from all parts of the body, e.g. from the forearm, by no means solely from the skull, whilst the late response could not be obtained from any other localization of the body than the skull and there best from the glabella and vertex.

What other proof, then, do we have that this late response *is not of a* non-specific character as the Bickford effect, the quick responses, are?

We feel that there is a fine proof involved in the detectability of the Stevens' power functions for the intensity functions obtained by our tech-

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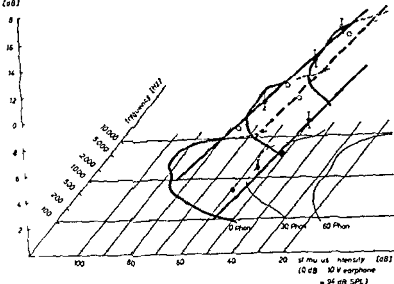


Fig. 4. Objective intensity functions in man for different frequencies and intensities in man. The foot points of them yield the "objective audiometric threshold curves"

proportional to the stimulus intensity with a given exponent, the numerical value of which is characteristic for that modality $y = x^n$ (magnitude of sensation equals intensity level and exponent n) (Stevens 1961). Those numerical values for pain, vibration of the skin, auditory stimuli, visual stimuli e.g. are 2.13, 0.96, 0.35, 0.21 respectively as shown in Fig. 2.

Now then there are subjective data obtained by means of psychophysical measurements. Sprengl & Ichioka of our laboratory, however, were able (in 1963) to show that for electrically elicited pain in man using the "objective" computer technique of averaging the stimulus locked responses within the human EEG the steepness of the intensity function is exactly of the same order as the one obtained by the Stevens group subjectively. This was the first realization of the old dream to be able to compare subjective and objective data in man. The next step led to the objective audiometry, first measuring again the total intensity function and comparing its steepness with that of the power functions. Again a fairly fine agreement of the numerical values could be obtained even for the adapted and the non adapted state (n 0.34–0.21 for non adapted and adapted states respectively).

Finally we succeeded in recording the objective intensity functions in man when using vibratory stimulation delivered by a ball vibrating at 60 cps to the palm of the right hand of a subject. Again good agreement of the steepness of both the objective intensity function and the subjective power function could be detected. For auditory stimulation only the late

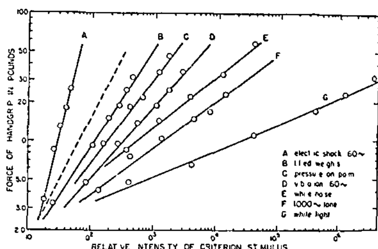


FIG 2 Stevens' power functions revealing different but consistent exponents of these "power functions" for a given stimulus modality The higher the numerical value of the exponent of the power function is, the steeper are the straight lines of the power functions in a double-logarithmic plot The steepest function is that for pain, the flattest one that for visual stimulation

nique when using stimuli of different modalities like light-flashes, auditory clicks, vibratory stimulation of the skin and electrically elicited painful sensations, again on the skin As Cramer stated, Plateau formulated and Stevens proved experimentally, the magnitude of sensations depends upon stimulus intensity in the way described in the law according to which the magnitude of sensation for any sensory channel and sensory modality is

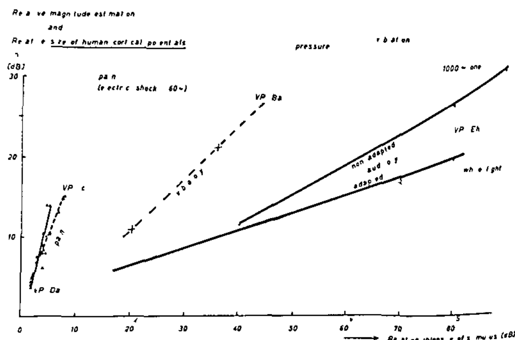


FIG 3 The steepness of the power functions for different modalities (pain vibration audition) obtained objectively (full lines) is identical with that obtained subjectively by the psychophysical technique (dotted lines instead of magnitude estimation read force of handgrip)

to project the cut of this plane with all intensity functions down to the frequency intensity plane. In this case those objectively measured curves of equal potentials agree fairly well with the subjectively measured ones of Fletcher Munson. This means that at all levels of size of potential objective audiometry can be performed based upon the technique of electronic averaging of the late cortical evoked response in man which we were able to describe here.

In conclusion it can be said that by means of the technique described in Athens in 1962 using the late cortical response with a latency of 150 msec it is possible to carry out objective audiometry in man. The advantage of this method is that it is practicable in young children too and in adults in all those cases where subjective audiometry is impossible. The possibility of a quantitative comparison of the objective and the subjective technique is based upon the fact that the total intensity functions gained through this technique agree in their steepness with the Stevens' power functions. Since they can be extrapolated easily (being straight lines) they enable us to get fairly precise absolute threshold curves in man. We are especially glad to see that our results in respect of the threshold curve are in agreement with those about which Dr. Davis reported in his paper today. A previous paper about this topic was given at the 7th International Congress of Audiology at Copenhagen on the 26th of August this year. About the "semi specific" character compare more detailed discussions (Keidel, 1964) especially in this volume (Davis, 1964).

RESUME

Des experiences avec les resultats des lents potentiels corticaux gagnes par les electrodes posees extracranialement a l'homme eveille (usage d'une speciale machine electronique) furent continuees. Les resultats:

1. La dependance du potentiel negatif (150 à 180 milli seconds apres le debut de la stimulation) de l'intensite de la stimulation montre pour quelques modalites (stimulation acoustique, vibratoire et douloureuse) des agrandissements caracteristiques qui correspondent aux resultats psychophysicaux (Plateau, Stevens).

2. L'agrandissement des fonctions de l'intensite est different pour les conditions adaptees et non adaptees comme les courbes audiometriques correspondantes chez l'homme normal.

3. Le mesurage electrophysiologique des seuils auditifs est possible avec les potentiels corticaux de l'homme.

ZUSAMMENFASSUNG

Frühere Experimente bei welchen am wachen Menschen extrakranial langsame reizsynchrone Rindenpotentiale mit Hilfe eines elektronischen Mittelungsverfahrens bei akustischer Reizung gewonnen werden konnten, wurden mit folgenden Ergebnissen weitergeführt.

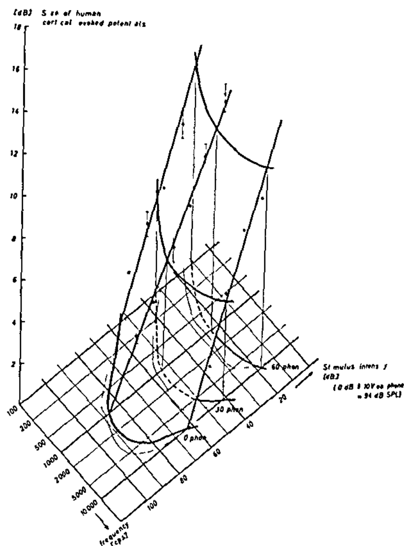


FIG. 5. The projections of the cuts representing planes of equal size of late evoked response in man with the objective intensity functions in man yield "objective curves of equal size of the late responses". Those curves (full lines) correspond fairly well with the subjective curves of Fletcher-Munson (dotted line). This procedure can be used for every wanted level of the late response electronically averaged according to the described technique in man.

response with a latency of 150 msec obeyed this law. All these facts are shown comparatively in Fig. 3.

Concerning the objective audiometry, additionally it only was necessary to vary the frequency of the sinusoidal tones across the whole bandwidth of hearing, what we did practically from 100 cps up to 10 kc on normal adult subjects of both sexes, to be able to show that the foot points of all auditory intensity functions yield the objective audiometric threshold curves as shown in Fig. 4.

Finally we compared, as one can see in Fig. 5, our curves (full lines) with the subjectively measured Fletcher-Munson curves (dotted lines) to show that it is also possible for a given size of evoked averaged potentials

J. Bordley. This question is directed to Drs. Davis and Keidel. Could you tell us what happens to this evoked potential under the influence of such drugs as curare and the barbiturates?

W. D. Keidel (Reply). I do not have any experience in this field of drugs at cortical level in man up to now. We did study, however, only the effect of kanamycin and streptomycinsulfate on the acoustic nerve as well as at cortical level in cat. For this I would like to refer to our publications in *Pflugers Archiv* during the last years.

H. Engstrom. I would like to join Dr. Bordley in stating that this has been an exceedingly interesting morning. It may be that some people have not understood everything that has been said. Still it has been important to show to us all these interesting and clinically important parameters of basic research. A question: In the cochlear nuclei there are very many nerve endings contacting one cell. Can you tell us why such a large amount of synapses is necessary?

Nelson Kiang (Reply). As Dr. *Engstrom* points out there are cells in the cochlear nucleus that are covered with many individual nerve endings. Assuming that these endings are from different fibers they may be simply the anatomical correlate of the physiological convergence suggested by our results. It may be that such a neuron will discharge only when a large number of endings are simultaneously activated performing some sort of averaging over all the endings. Random discharges of individual fibers would not be correlated and would thus fail to elicit a response.

J. E. Desmedt. The very interesting report of Dr. Davis is particularly appreciated by those who have followed the controversy about the muscle *vs* brain origin of the acoustic evoked potentials recorded from the scalp. As pointed out by Dr. Davis there may be good anatomical reasons for the difficulty experienced in obtaining evoked potentials from the deeply lying auditory cortex in man. From a practical point of view it may prove invaluable to assess the type of evoked activity he has studied as a check on more conventional audiology.

I am wondering whether these potentials which have now been so clearly demonstrated may not be somehow related to the so-called "Vertex potential" described in 1953 by Y. Gastaut and by J. Bancaud, V. Bloch & J. Paillard (*Revue Neurologique Paris*, vol. 89, pages 488–518). These vertex potentials apparently disclose a similar latency and are also recorded from the vertex. They can be large when the stimulus is unexpected and they habituate rapidly when repeated.

L. B. W. Jongkees. I should like to ask Dr. Davis whether the parallelism he generally finds between the electrical effects following a stimulus and its conscious perception is the rule or whether he has sometimes found clear deviation between the two different effects of stimulation.

H. Davis (Reply). The relation of the threshold of detection of the evoked response to subjective threshold is not exact. With normal young adults the latter is lower by 10 to 25 dB. With our hard-of-hearing children the correspondence is much closer. I do not know exactly why. Most of the differences are no greater than the uncertainty of the method.

If a normal subject is preoccupied with the material that he is reading he may deny that he has heard any clicks and yet the oscilloscope shows a response.

H. Portmann. It was one of the most interesting mornings I had about the problem of evoked potential in audiology. I only want to ask the panel one question. Do you think that this method is sufficiently ready at the present time

1 Intensitätsfunktionen der zweiten oberflächennegativen Komponente (Latenz 150 bis 180 msec) in doppeltlogarithmischem Massstab zeigen für verschiedene Reizmodalitäten und Qualitäten (akustische, vibratorische und Schmerzreize) verschiedene, charakteristische Steilheiten, die mit dem psychophysisch gemessenem dem Plateauschen Gesetz gehorchenden gut übereinstimmen

2 Die Steilheiten adaptierter und nicht adaptierter akustischer Intensitätsfunktionen unterscheiden sich wie die entsprechenden audiometrischen Kurven von Normalpersonen

3 Die für Sinustöne verschiedener Frequenz gewonnenen Intensitätsfunktionen dieser Rindenpotentiale schneiden die Schwellenebene in derselben Form wie die subjektiv gewonnene audiometrische Kurve

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REFERENCES

DAVIS H 1965 Slow cortical responses evoked by acoustic stimuli [Paper given at the Collegium ORLAS Würzburg 1964] *Acta Otolaryng (Stockh)* 59 179 185

KEIDEL W D 1959 Elektronisches Rechenwerk zur Mittelwertsbildung statistisch streuender periodischer bioelektrischer Potentiale *Z Biol* 111 54 66

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KEIDEL W D and SPRENG M, 1963 Elektronisch gemittelte langsame Rindenpotentiale des Menschen bei akustischer Reizung [Paper given at the Collegium ORLAS Athens 1962] *Acta Otolaryng (Stockh)* 4 56 318 328

SPRENG M and KEIDEL W D 1963 Neue Möglichkeiten der Untersuchung menschlicher Informationsverarbeitung *Kybernetik* 1 243 249

SPRENG M and ICHIOKA M 1964 Langsame Rindenpotentiale bei Schmerzreizung am Menschen *Pflugers Arch* 279 121 132

STEVENS S S 1961 The psychophysics of sensory function In *Sensory communication* (ed W A Rosenblith) Wiley New York

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DISCUSSION AFTER THE ROUND TABLE CONFERENCE

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Nelson Kiang (Reply) There is of course no clear answer to Dr *Shambaugh's* question at this time but I venture to suggest that part of the answer lies in the nature of the acoustic signals that constitute speech It is only in vowel sounds that one finds acoustic components that resemble tones The critical features of consonants and transitions between vowels and consonants are not considered in pure tone audiometry The time patterns of neurons to such transient stimuli may well be disrupted by pathological conditions Perhaps scattered damage to neurons would cause such disruptions but would leave sufficient representation to result in normal pure tone audiograms

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REFERENCES

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Spreng, M. and Keidel, W. D. 1963. Neue Möglichkeiten der Untersuchung menschlicher Informationsverarbeitung. *Kybernetik*, 1, 243–249.

Spreng, M. and Ichioka, M. 1964. Langsame Rindenpotentiale bei Schmerzreizung am Menschen. *Pflügers Arch.*, 279, 121–132.

Stevens, S. S. 1961. The psychophysics of sensory function. In *Sensory communication* (ed. W. A. Rosenblith). Wiley, New York.

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CENTRAL REGULATION OF THE VESTIBULAR SYSTEM

J J GROEN
Utrecht, The Netherlands

From the O.R.L. Department (Head Prof P G Gerlings), Utrecht State University

Stimulation of the vestibular organs generates in a limited range stimulation-proportional activity, which is modified under influence of the central nervous system by two mechanisms (1) inhibition, (2) pattern centre interference. Inhibition appears to be a postnatal acquired property as is shown by a series of measurements of eye deviations in new born dogs and infants. Pattern centre activity presumably originates during the same period preceded by development of nystagmus.

INTRODUCTION

Some time ago (Groen 1963) we reported on a series of vestibular measurements on new born dogs and a human baby. Since then we continued the experiments on other litters. Another infant was also investigated. Altogether have now been examined on vestibular reactions since birth 13 dogs and 2 human babies. It has been our aim to follow the vestibular phenomena after birth in order to see how the different aspects, eye deviation, nystagmus and inhibition comported themselves. It will appear in the new results, to be discussed later on, that the main trends of the former investigation are confirmed. Now we can avail ourselves of more material and some of the trends can be studied in greater detail.

METHOD

In our laboratory is a circular rotating room (inside diameter 270 cm, height 220 cm) which can maintain a constant velocity between 1 and 120° sec over any period of time. It provides ample space for three people and a test subject. The driving controls are inside the room, the operator turns together with the test subject.

The usual procedure for vestibular stimulation during the experiments described here has been the following. The animal (or the baby) is kept in a fixed position in which mainly the horizontal canal pair is stimulated. The room is slowly accelerated until the desired angular velocity is obtained. The turning is then continued with this velocity value until the test subject is in perfect equilibrium; the eyes is at rest in its median position and stays there. Then the room is stopped within 2 seconds, without any abruptness. The after phenomena are then observed through Frenzel glasses. The room

to be used as a routine technic for objective audiometry in a good clinical audiological center?

H. Davis (Reply): The equipment for recording auditory evoked responses can now be purchased by those who have the price The cost is comparable with that of an electron microscope. The computer is less expensive alone if you have the electroencephalograph and the acoustic stimulating equipment I predict that within two years simpler equipment, designed for this specific purpose and less elaborate than our research units, will be available.

E. Bocca Dr. Yuan sheng Kiang's paper and some of Dr. Davis' remarks raised the greatest interest on my part. In studying the troubles of the auditory integration in cases of "central" hearing defect the problem which presents itself to us again and again and which is the most difficult to find a solution for, is that of *where* different types of analysis (for time, intensity, frequency etc) may take place Some pharmacological tests carried out upon man seem to suggest that drugs acting at a different level may mainly affect this or that type of analysis

Now micro-electrode technics allow a deeper and deeper insight into not only the type, but I hope soon, also the level of different types of analysis

May I ask both speakers if they think that in the future they will be in a condition to suggest some particular type of acoustical stimulation to be used in psychoacoustic research in order to bring out finer troubles of analysis with a localizing value?

Nelson Kiang (Reply) Although work on animals may provide some clues to the nature of certain types of hearing defects, the ultimate job of correlating behavioral loss with lesion belongs to the clinics using data from humans, to the otologists, audiologists and pathologists Such a program would be difficult although not impossible to organize

H Davis (Reply) For assistance to neurosurgery we must rely on purely empirical correlations that are established by careful study and testing of patients and relating the results to pathological anatomy as determined at operation or post mortem This method is slow and expensive, but it is the only one Neuropharmacology gives answers in physiological terms, not anatomical Drugs tend to affect entire systems in the central nervous system, and these sub systems are closely intermingled in their anatomical distributions

G E Tremble As a clinician I have been very much impressed with this presentation A question I would like Dr Davis to answer if possible is why do we see so frequently that the primary dip in an audiogram is at the 4096 dB level

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CENTRAL REGULATION OF THE VESTIBULAR SYSTEM

J. J. GROEN
Utrecht, The Netherlands

From the O R L. Department (Head: Prof P. G. Gerlings), Utrecht State University

Stimulation of the vestibular organs generates in a limited range stimulation proportional activity, which is modified under influence of the central nervous system by two mechanisms. (1) inhibition, (2) pattern centre interference. Inhibition appears to be a postnatal, acquired property as is shown by a series of measurements of eye deviations in newborn dogs and infants Pattern centre activity presumably originates during the same period preceded by development of nystagmus.

INTRODUCTION

Some time ago (Groen, 1963) we reported on a series of vestibular measurements on new-born dogs and a human baby. Since then we continued the experiments on other litters Another infant was also investigated. Altogether have now been examined on vestibular reactions since birth, 13 dogs and 2 human babies It has been our aim to follow the vestibular phenomena after birth in order to see how the different aspects, eye-deviation, nystagmus and inhibition comported themselves It will appear in the new results, to be discussed later on, that the main trends of the former investigation are confirmed Now we can avail ourselves of more material and some of the trends can be studied in greater detail.

METHOD

In our laboratory is a circular rotating room (inside diameter 270 cm, height 220 cm), which can maintain a constant velocity between 1 and 120°/sec over any period of time It provides ample space for three people and a test subject The driving controls are inside the room, the operator turns together with the test subject

The usual procedure for vestibular stimulation during the experiments described here has been the following The animal (or the baby) is kept in a fixed position in which mainly the horizontal canal pair is stimulated. The room is slowly accelerated until the desired angular velocity is obtained. The turning is then continued with this velocity value until the test subject is in perfect equilibrium, the eye is at rest in its median position and stays there Then the room is stopped within 2 seconds, without any abruptness The after-phenomena are then observed through Frenzel glasses The room

to be used as a routine technic for objective audiometry in a good clinical audiological center?

H. Davis (Reply): The equipment for recording auditory evoked responses can now be purchased by those who have the price The cost is comparable with that of an electron microscope. The computer is less expensive alone if you have the electroencephalograph and the acoustic stimulating equipment I predict that within two years simpler equipment, designed for this specific purpose and less elaborate than our research units, will be available

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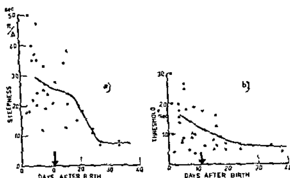


Fig 1 Test subjects dogs Π Δ (in seconds) and threshold (in °/sec) as a function of time (in days after birth) After 16 days there is a marked trend downwards ending in a constant Π Δ value of about 7 seconds A similar course (*b*) shows the threshold Central influences, in the form of inhibition, seem to be fully developed 27 days after birth The lines represent the arithmetical means of the measurements The arrows indicate the moment of spontaneous opening of the eyes

a sharp drop to 15 seconds on the 24th day, going further down to 7 5 seconds to stay there from the 27th day onwards

In the meantime the eyes had opened spontaneously on the 11th day (see arrow) This, apparently, has no major influence

The large values of the standard deviation are caused by the differences in behaviour of the animals Animals of one litter may differ somewhat but different litters show more deviations amongst each other The general trend, however, is the same for all dogs An exceptional dog is shown in Fig 2, even after 80 days, its Π/Δ stayed at 16 seconds, with a normal threshold of 4°/sec It is not impossible that there are dogs which keep a steep cupulogram similar to humans who are inclined to seasickness

The threshold shows a similar course as a function of time It starts at the 2nd day around 5°/sec rising to a value of 14°/sec on the 7th day whereafter a gentle decline back to 5–6°/sec

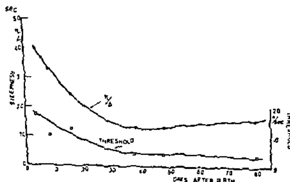


Fig 2 This dog although showing the same trend as the others, ends up with a rather high Π Δ (about 15 sec) but a normal threshold (4° sec)

is kept in darkness; only the dials of the controls of the speedometer and of the stopwatch on the panel of the operator are illuminated

In order to observe the eye of a new-born dog, the eyelids of one eye are slit open. They are kept open during the experiment by surgical wire, which is afterwards removed A very small piece of cigarette paper is stuck on the cornea. This tiny white spot enables the observer to notice the slightest movement of the eyeball. It has to be replaced several times when a dog is very young The eye deviations are very large so that the spot often disappears into the eye corner It sometimes will stick there, so it has to be brought into position again.

The eye of a young infant is observed by opening gently the eyelids with two fingers. Again, the rotation is observed with Frenzel glasses This is easy in the human test subject, but almost impossible in the dog, hence the necessity of a white spot

We usually started with a weak stimulus, e g. 30°/sec If the response was favourable we continued with smaller values until no eye movements could be observed any more We then repeated the first measurement and proceeded with stronger stimuli. The largest value used as a rule in these series has been 60°/sec. In exceptional cases we went as high as 80°/sec The stimuli were presented alternately clockwise and anti-clockwise A complete series of measurements on a dog took about two hours, whereas the human baby only needed half an hour.

Results on Dogs

The vestibular phenomena in dogs were observed in the period of 3 hours after birth until they were 33 days old. With some dogs the experiments were continued up to 80 days We did not succeed in obtaining useful results before the 2nd day after birth, although we tried several times to get them at an earlier stage During each session we tried to obtain a series of results which informed us of the *status quo* of the development of the function of the vestibular-ocular tract Such measurements have been demonstrated in the earlier report (Groen, 1963) As we can avail ourselves now of more data, we have plotted the averages for all the dogs of the two characteristic values Π/Δ and threshold in separate diagrams as a function of time (Figs 1 *a* and 1 *b*) The value Π/Δ denotes the steepness of the cupulogram and is expressed in seconds The threshold is expressed in degrees per second, being the minimum impulse which produces a just noticeable eye deviation The steepness tells us about the rate of decline of the vestibular-ocular phenomena If the steepness is large (> 20 sec), then the decline is slow (as in very young animals) If the steepness is small (< 10 sec), the decline is more rapid (older and more experienced animals)

The Π/Δ curve starts at the 2nd day on an average of 20 seconds, rising to 30 seconds with a large standard deviation on the 5th day, going back slightly to 27–25 seconds in the following period up to 16 days, whereafter

cases Inhibition starts to come in effectively around the 25th day to be completed after 60 days It can be noticed, however, for stronger stimuli (>30°/sec) on the 16th day already Whether the child is asleep or awake does not affect the value of the duration of the after-phenomena There is, however, this difference during sleep, eye deviations prevail, whereas nystagmus is usually present when the child is awake

CONCLUSION

The development of the function of the vestibular-ocular system shows the following aspects

1 Immediately after birth not much can be said by us about ocular responses to vestibular stimulation in dogs In man some activity may occur

2 Vestibular control on the ocular tract develops rapidly Two days after birth it has almost reached its complete function During the first 16 days after birth the vestibular command on the eyes seems to be uninfluenced by other agents in dogs, producing constant deviations or periodically intercepted ones (= nystagmus)

3 The nystagmus centre starts its interference haltingly around the 3rd day increasing its grip on the vestibular-ocular tract until it is usually fully developed after 3 weeks in dogs

4 In dogs central influences of extra-vestibular origin tend to appear at the end of the first week, after 4 weeks its interference is fully active The change in steepness of the response curves is a good criterion If we take 25 seconds as a mean value during the first 16 days, 7 seconds will be the ultimate average after 4 weeks, which means a reduction by a factor of roughly 4 In the human test subject this reduction is about a factor of 2 5

5 The transformation of the signals, originating from the vestibular organs and expressing themselves in eye movements, is under the constant control of an extra vestibular centre producing inhibition in the adult test subject

6 Thus we have to accept this fact that whatever experiment on a vestibular organ system is carried out it will ever yield results which are strongly tainted by extra vestibular interferences

ACKNOWLEDGEMENT

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RESUME

La stimulation des organes vestibulaires produit dans une mesure limitee, une activite proportionelle a la stimulation modifiee sous l influence du systeme nerveux central par deux mecanismes (1) inhibition, (2) interference du centre

Eye-Deviation, Nystagmus and Inhibition

The after phenomena following the impulse administered, usually were merely eye-deviations. Only once did we observe some nystagmus strokes in dogs $3\,^1/_2$ days after birth. The duration of a nystagmus fitted into those of the deviation measurements. In the course of time more and more nystagmus strokes (or series of strokes) were observed, but it usually took 3 weeks before the tendency to a mere deviation disappeared. As it does not seem to matter from the point of view of duration, whether the stimulated condition of the vestibular apparatus expresses itself by deviation only or by periodically intercepted deviations (= nystagmus), we can take either symptom as a criterion for vestibular reaction. Thus we can conclude from Fig. 1 that in dogs, immediately after birth, no effective vestibular control is exerted on the eyes. This control starts to grow until it can be measured by us on the 2nd day, it reaches its maximum activity already on the 5th day. Between then and the 16th day it has a monopoly whereafter another mechanism comes into the foreground: the inhibition. After 27 days this inhibitory mechanism appears to be fully developed.

The first tendency to inhibition was noticed by us on the 6th–7th day for strong stimuli in some dogs, but not in all. Later on inhibition showed its influence already for one single stimulus of 30°/sec, inhibition was then developed into a general condition in all dogs.

The New-born Babies

In Fig. 3 the corresponding data for the human test subjects have been plotted. The same general trend as in dogs can be found, merely the time scale is different.

We seem to be about twice as slow in vestibular development as dogs, but we attain the same values for steepness and are more sensitive with regard to threshold. Nystagmus may be present on the first day after birth but it usually develops in the course of time. Again, it may appear in a series of stimuli which hitherto produced mere deviations. The duration of the after-phenomenon, be it a nystagmus or a deviation, is the same in both

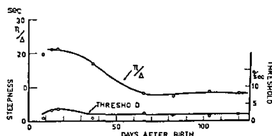


Fig. 3. Human test subjects: Π/Δ and threshold have been plotted in the same diagram as a function of time. Maturation seems to take place about twice as slowly as in dogs. Inhibition completed in 2 months.

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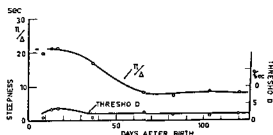


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bekannten Mitteln gegen Seekrankheit wohl die subjektiven Erscheinungen abnehmen während die objektiven Erscheinungen sich sogar verstärken Auch das unbewußte Gedächtnis', das in letzter Zeit mehrfach genannte memory' ist zu bedenken Herr Groen erwähnte bereits den Seemannsgang d h das breitbeinige Gehen des Seemannes an Land der offensichtlich noch das Gefühl hat, er würde sich auf hoher See befinden Auch die Tatsache, daß die vestibuläre Übererregbarkeit nach einer Alkoholintoxikation noch festzustellen ist zu einem Zeitpunkt an dem die unmittelbare pharmakologische Wirkung sicherlich schon abgeklungen ist spricht dafür, daß es sich zu diesem Zeitpunkt noch um eine Enthemmung handelt (Jatho)

Bei der Hemmung scheinen demnach anatomisch physiologische, pharmakologische aber schließlich auch psychologische Momente eine Rolle zu spielen Ich möchte Herrn Groen fragen, ob er bei seinen Untersuchungen auch Beobachtungen über vegetative Erscheinungen hat machen können

H Davis In your abstract you describe inhibition in the vestibular system as a postnatal acquired property In your talk you spoke of memory' in this system In the legend of one of your figures you used the word maturation Just what do you mean? Is the inhibition acquired as the result of sensory experience or does it develop spontaneously as a result of the continuing development of the central nervous system which is still quite immature at birth?

S H Mygind More than 50 years ago I worked on the same problems I should like to call attention to the otolith reflexes in new born children observed when the babies are kept lying on their abdomen They always try to stretch the head upwards with a deviation of the eyes in the same direction and a wrinkling of the skin of their foreheads These reflexes disappear in a few days In mammals they continue for ever It is the same mechanism of inhibition due to the evolution of regulating influences of the higher parts of the central nervous system, the same which comes into play in the compensatory process after destruction of the labyrinth

F Huizinga Daß es eine zentrale Regulierung des Vestibularissystems gibt, ist sicher nicht neu Es ist gut hier in Deutschland der Arbeit von Barany-Wittmaack zu gedenken Sie sprachen von Ausfall und Erregungsdekompensation Und dann vom Nystagmus von Bechterew Das alles ist doch sicher zentral Wohl neu und sehr original ist diese postnatale Hemmung beim Kind und Tier Und sicher original ist die Weise in der das präsentiert wurde Ich schätze diese sehr Eine Frage Was ist eigentlich die Bedeutung dieser Hemmung?

I B W Jongkees Jongkees points to the influence of a sinusoidal movement given to a pigeon Many hours afterwards the sinusoidal movements, with the same frequency could be found back within the normal random distribution of the movements of a pigeon s head (Klijn)

The same phenomenon is observable in patients who are subjected to electronystagmography after having been calibrated by looking at a swinging pendulum (Philipson)

J J Groen (Reply)

V M Arslan We did examine the vertical canals as well, and their behaviour was essentially the same as that of the horizontal canals The results will be published elsewhere

Ge G Kelemen In humans we found that the reactions, e g to clockwise stimulation were systematically stronger (longer lasting) than to counter clockwise

patron. L'inhibition semble être une propriété postnatale acquise comme il est démontré par une série d'expérimentations sur des chiens et des enfants nouveau-nés de la déviation de l'œil. L'activité du centre patron commence pendant la même période, précédée par le développement du nystagmus.

ZUSAMMENFASSUNG

Reizung der vestibulären Organe ergibt in einem beschränkten Bereich eine proportionale Aktivität, welche unter dem Einfluß des zentralen Nervensystems auf zwei Weisen modifiziert wird: 1. Hemmung, 2. Interferenz von zentralnervösen Aktivitätsmustern. Hemmung scheint eine postnatal errungene Eigenschaft zu sein, wie eine Meßreihe der Augenabweichungen bei neugeborenen Hunden und Kinder zeigt. Interferenz von zentralen Aktivitätsmustern entwickelt sich wahrscheinlich in derselben Periode, welcher die Entwicklung des Nystagmus vorausgeht.

REFERENCES

GROEN, J. J. 1963. Postnatal changes in vestibular reactions. *Acta Otolaryng.* (Stockh.) 56, 390–396.

30 Marislaan, Utrecht, The Netherlands

DISCUSSION

M. Arslan: To add to the very interesting results of Dr. Groen the data obtained by Dr. Giorgio. The vertical canals reveal their excitability only some months after the birth. In the first days of life only the lateral canal has its reflex function present. The difference between the two canal systems can be explained hypothetically with ontogenetic processes.

G. Kelemen: To the question "memory" of the vestibular system: (*a*) A dog will stay away from a turntable after one testing. (*b*) Vestibular tests done on persons in deep general anaesthesia leave as an aftereffect dissociation among others in reaction of the right and the left side—offering problems in general vestibular physiology and concerning the question of handedness.

R. Mittermaier: Herr Groen hat uns über die lebhaften Nystagmusreaktionen beim Säugling berichtet und daß es offensichtlich erst allmählich zu einer Hemmung der anfangs so lebhaften Reaktion kommt. Kleinkinder sollen nun weitgehend unempfindlich sein gegenüber den vestibulären Erregungen bei Seereisen, während im späteren Alter die Kinder ja in ganz besonderem Maße zu Reisekrankheiten neigen. Offensichtlich kommt es erst durch die postnatale Markreifung zur funktionellen Verbindung zu den vegetativen Zentren. Aus dem nystagmischen Fremdreflex der vestibulären Reaktion beim Säugling entsteht erst später der mehrfach von anderen Stellen her gesteuerte Reflex. Im höheren Alter sind die Menschen gegenüber starken vestibulären Reizen weniger empfindlich als in jüngeren Jahren (Arslan, Rossberg). Die objektiven Reaktionen fallen vergleichsweise schwächer aus *und auch die vegetativen Reaktionen sind* abgeschwächt. Die Neigung zur Seekrankheit nimmt, wie man häufig hört, ab. Unter dem Begriff der Hemmung verbergen sich zweifellos sehr verschiedene Momente. Zu erwähnen ist u. a., daß unter dem Einfluß von Barbituraten oder den

DIE VERÄNDERUNGEN AN DER RESPIRATIONSSCHLEIMHAUT DER RATTEN BEI EXPERIMENTELLEN HYPOTHYREOIDISMUS[1]

B. GUŠIĆ, B. FEMENIĆ, J. LAKIĆ, N. RILS und V. KONIĆ-CARNELUTTI
Zagreb, Jugoslawien

Aus der Otolaryngologischen Klinik (Dir.: Prof. Dr. B. Gušić) und dem Physiologischen Institut (Dir.: Prof. Dr. N. Allegretti) der Medizinischen Fakultät der Universität Zagreb

Die Trachealschleimhaut mittels Propylthiouracyl/PTU behandelter Ratten wurde einer histologischen Untersuchung unterzogen und dabei eine papilläre Hyperplasie des Epithels mit verstärkter Funktion der Becherzellen und eine kleinzellige Infiltration mit Ödem im Bereiche der Lamina propria festgestellt. Es wird versucht, diese Resultate mit klinischen Befunden beim Menschen in Einklang zu bringen.

Obzwar das klinische Bild an der Nasenschleimhaut bei der Hypofunktion der Schilddrüse, namentlich nach den Arbeiten von Laskiewicz, Nager, Proetz und Walsh, nicht mehr unbekannt geblieben ist, bedürfen die wechselseitigen Beziehungen der Schilddrüsenhormone und der Respirationsschleimhaut noch mancher Aufklärung. Dies hat uns veranlasst, innerhalb unserer Untersuchungen an der Respirationsschleimhaut, die wir schon jahrelang durchführen, zu versuchen, an Tieren die künstlich in eine Hypothyreose gebracht worden sind, diese Veränderungen histologisch zu verfolgen.

Wir haben für unsere Untersuchungen die Trachealschleimhaut gewählt, weil sie sich gegen äussere Einflüsse viel widerstandsfähiger gezeigt hat als die Nasenschleimhaut, wie dies die neuesten Untersuchungen von Hilding sehr eindeutig gezeigt haben und wir es nur bestätigen konnten. So konnten wir an allen unseren Versuchstieren an der Septumschleimhaut ein Verschwinden der Zilien und eine Abschuppung und mehr oder weniger hochgradige Metaplasie des Epithels mit Anschwellung der kollagenen Faser beobachten, die in einigen Fällen auch mit einer Hypertrophie der epithelialen Drüsenelemente und papillärer Hypertrophie gepaart war. Diese Veränderungen entsprachen vollkommen den Befunden, die Proud an seinen Versuchstieren (Hunden) nach partieller oder totaler Thyreodectomie feststellen konnte. Gleichzeitig aber fanden wir ganz ähnliche Veränderungen auch an der Septumschleimhaut unserer Kontrolltiere, ja in einem Falle sogar eine extreme Atrophie der ganzen Mucosa. Unsere Auffassung

[1] Diese Arbeit wurde durch die finanzielle Unterstützung des staatl. jugoslawischen Fonds für die Förderung der wissenschaftlichen Arbeit ermöglicht.

stimulation during a special session. However, next month this predominant behaviour might be just reserved to the counter-clockwise direction

to *R. Mittermaier:* We have had the opportunity to study human and animal reactions on an Ocean-going vessel. It appeared that very young children were sensitive to seasickness in many instances, as were young dogs and cats on board.

to *H. Davis:* I think that the eventual inhibition is an acquired property through training (sensory experience), made possible by the continued development of the nervous system after birth. With "maturation" I mean development into a complete system of organ-nervous connections and feedback. With "memory" I mean that property of the (hypothetical) "pattern centre" which enables us to get adapted to any type of repetitive motion (e g ship).

to *S. H. Mygind* Of course I agree with your remarks on behaviour of animals and human test subjects after repeated stimuli.

to *E. Huizinga* Inhibition, seen as a curtailment of after-phenomena, seems to be the appropriate answer to our daily needs. The after-effects of one stimulation should not interfere with the vestibular control of the next.

to *L. B. W. Jongkees* I am most grateful that my supposition on the existence of a pattern centre has been proved to be true, almost "accidentally".



Abb. 3. *Feine basale Membran* ohne Verdickung und ohne Anzeichen irgendwelcher Sedimentation. Trachea der Ratte in Hypothyreose

Abb. 4. Leichtes Ödem in der Submucosa der *Trachealschleimhaut* der hypothyreotischen Ratte mit kaum angedeuteter Kleinzelleninfiltration

ma Kali Chemie, Hannover) auf 100 *g ihrer Standard*nahrung gefüttert, was einer Tagesdosis von 25 mg pro Tier entspricht. *Der Sauerstoff*verbrauch (*O*$_2$) wurde zuerst alle 7 Tage *und dann* später alle 14 Tage regelmässig gemessen. Eine signifikante Herabsetzung des *Körper*gewichtes und des Verbrauches an Sauerstoff konnte vom *13. Tage* an nach Anfang des Experimentes an festgestellt werden (Abb. 5 *und 6*).

Die Tiere, je zwei von jeder Gruppe, wurden *in fol*gender Reihenfolge (Tab. 1) geopfert und die Trachealschleimhaut sowie *die Schilddrüse* so-



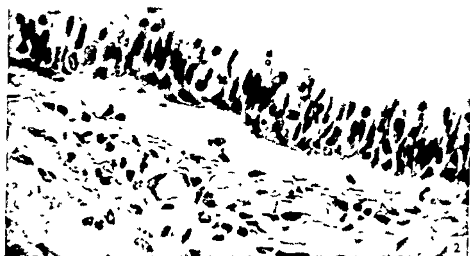


Abb. 1. Herabsetzung des Flimmerepithels an der Trachea bei hypothyreotischen Ratten
Abb. 2. Aktive Tätigkeit der intraepithelialen Drüsen bei Ratten in Hypothyreose

besteht darin, dass es sich in allen diesen Bildern nur um verschiedene Phasen ein und derselben, für die Respirationsschleimhaut charakteristischen, *Reaktionsart handelt, wobei die Art des Reizes von untergeordneter* Bedeutung ist. Diese, wir könnten fast sagen Überempfindlichkeit der Nasenschleimhaut auf äussere Reize, hat uns dann genötigt, für unsere Zwecke die Trachealschleimhaut zu verwenden.

Es wurden 32 drei Monate alte männliche Albinoratten einheitlichen VM-*Ursprunges von 220–300 g Körpergewicht genommen und von diesen nach* der Methode der zufälligen Auswahl 16 als Kontrollgruppe unter gewöhnlicher Nahrung belassen.

Die übrigen 16 wurden mit 0,2 g Propylthiouracil (PTU-Propycil „Rhena-

TABELLE 1. *Die Reihenfolge der Tieropferung und ihre Befunde*

Tieropferung (nach Tagen)	Befund
7	Keine sichtbaren Veränderungen an der Schilddrüse
14	und an der Trachealschleimhaut
21	Stellenweise angehender Zerfall des Flimmerepithels
28	mit Herabsetzung der Epithelhöhe
42	Leichtes Ödem der Submucosa mit angedeuteter
56	Kleinzelleninfiltration
94	Verstärkte Tätigkeit der intraepithelialen Drüsen
133	mit vollkommenem Zerfall der Zilien

Ödem mit stellenweise kaum angedeuteter Kleinzelleninfiltration festgestellt werden. Dabei erscheint bemerkenswert, dass diese Befunde in der Submukosa in keinem direkten Verhältnis zu der Intensität bzw. der Zeitdauer der Hypofunktion der Schilddrüse zu stehen scheinen, sondern mehr ein Ausdruck streng *individueller Reaktionsfähigkeit* jedes einzelnen Tieres auf die Verminderung der Schilddrüsenhormone darstellen, was *wieder auf eine* breite, ganz individuell veranlagte Reaktionsfähigkeit der Trachealschleimhaut des einzelnen Tieres hinweist.

Wenn wir jetzt versuchen wollen, unsere Befunde an der Trachealschleimhaut der Ratten mit den bis jetzt beschriebenen klinischen Befunden an der Nasenschleimhaut des Menschen in Einklang zu bringen, so müssen wir feststellen, dass sich diese Befunde ziemlich unterscheiden. Der Grund dürfte vorwiegend in der mehr komplexen und komplizierten Funktion der Nasenschleimhaut zu suchen sein, wobei die *Vorgänge an* der Basalmem*bran, die Vaskularisation und die autonome Innervation* eine hervorragende Rolle spielen. Dass es sich um Vorgänge handelt, die von allergischen ver-

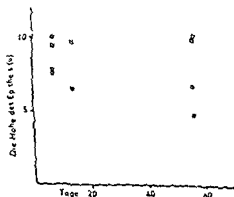


Abb. 7. Die Höhe des Follikelepithels der Schilddrüse bei normalen (○) und hypothyreotischen (□) Ratten.

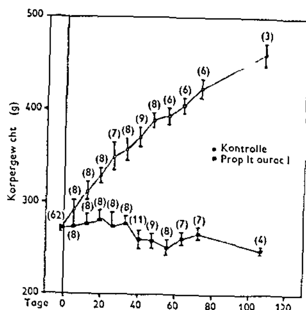


Abb 5 Das Körpergewicht der normalen (O) und hypothyreotischen Versuchstiere (■) In Klammern die Zahl der Versuchsratten

gleich präpariert Bei allen mit PTU gefütterten Tieren konnte an der Thyreoidea eine signifikante Höhenvergrösserung des Follikelepithels fest gestellt werden, was als ein sicherer Beweis der Hypofunktion dieser Schilddrüse zu bewerten ist (Abb 7)

Bei den am 7 und 14 Tage nach der Einführung des Experimentes geopferten Tieren konnten in der histologischen Struktur keine Veränderungen gegenüber den unbehandelten Tieren verzeichnet werden, was auch dem Befund an O_2 vollkommen entspricht Bei allen folgenden Gruppen, von den nach 3 Wochen weiter geopferten, konnte eine signifikante Herabsetzung des Flimmerepithels bei einer aktiven Tätigkeit der intraepithelialen Drüsen in den histologischen Schnitten bemerkt werden Die basale Membran zeigte keine Verdickung Auch sind an ihr keine Anzeichen irgend welcher Sedimentation zu bemerken In der Submukosa konnte ein leichtes

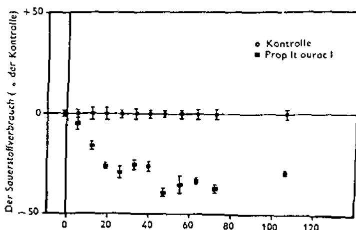


Abb 6 Der Sauerstoffverbrauch bei normalen (O) und hypothyreotischen (■) Ratten

ÉTUDE DES FIBRES NERVEUSES AMYÉLINIQUES DE LA CORDE VOCALE

P. ARDOUIN et M. MAILLET
Tours, France

Les auteurs expérimentant sur le larynx de l'homme et de certains mammifères décrivent les terminaisons des fibres nerveuses amyéliniques telles qu'ils les ont observées au niveau du muscle vocal et de la muqueuse de la corde vocale.

Les histologistes et les physiologistes connaissent bien l'importance morphologique des terminaisons nerveuses au niveau du muscle strié en général et les laryngologistes n'ont pas manqué d'exercer leur sagacité sur l'étude microscopique du muscle vocal. Il semble que la neuro-physiologie du larynx ait subi depuis quelques temps un renouveau d'activité.

Cependant après les études remarquables de Georges Portmann, de J. Terracol, de Sir Victor Negus, de Ruedi, d'Aubry et Vallencien, de Berendes, d'Arslan et d'autres auteurs, les laryngologistes s'affrontent encore sur la valeur respective de la théorie tonique classique et de la théorie clonique, telle que la comprend Husson.

Plus récemment les auteurs ont dirigé leurs recherches vers la possibilité d'une fonction proprioceptive de la part de la musculature laryngée comportant la présence d'une innervation sensitive. Il s'agit en fait des fuseaux neuro-musculaires.

Cette nouvelle notion est intéressante car elle permettrait d'envisager la réalité d'un véritable système d'auto-régulation contractile de l'ensemble des muscles du larynx *en fonction des excitations fournies par le muscle vocal lui-même*.

Au dernier Congrès de Phonologie Expérimentale le Professeur Arslan et ses élèves sont venus nous apporter sur ce sujet le point de vue très pertinent de l'École de Padoue.

D'autre part, le Professeur Terracol dans son étude récente sur la morphologie fonctionnelle du larynx a parfaitement décrit les fuseaux neuromusculaires au niveau du muscle vocal à la suite des travaux de Winckler et de Vincento Roberto.

Enfin plus récemment Rossi et Cortesina, de Turin, ont repris cette question en insistant sur la diversité d'opinion des auteurs et en signalant la position spéciale de Goerttler qui décrit ces formations nerveuses proprioceptives du muscle vocal sous le nom de *terminaisons myofibrillaires endogènes*.

schieden sind, beweist gerade der Befund an der Basalmembran die nirgends auf unseren Präparaten eine Verdickung oder sonst eine sichtbare Veränderung aufweist, sondern überall gleichmässig dünn erscheint Von den durch äussere Reize bedingten Veränderungen in der Trachealschleimhaut unterscheiden sich unsere Befunde durch eine kaum angedeutete Kleinzelleninfiltration in der Submukosa die wenn vorhanden fast ausschliesslich in dem membranösen hinteren Abschnitt und nicht entlang des Perichondriums in Erscheinung tritt und von der sonst üppigen Kleinzelleninfiltration bei äusseren Reizen, die das Bild dort vollkommen beherrscht stark abweicht

SUMMARY

A histological study of the tracheal respiratory mucosa of rats which received propylthiouracil was performed This investigation revealed papillary hyperplastic changes of the respiratory epithelium with increased activity of the intraepithelial glands Round celled infiltration and oedema in the lamina propria of the respiratory mucosa was proved as well The authors try to find a relationship between these experimental results and the clinical findings in man

RESUME

L examen histologique de la muqueuse tracheale des rats traités avec propylthyouracyl montre une hyperplasie papillaire de l epithelium La fonction des glandes intraepitheliales est augmentee, tandis que dans le tissu de la lamina propria se forme un proces oedemateux accompagné par une infiltration des cellules inflammatoires Les resultats sont discutees et comparées avec des examens cliniques chez l homme

LITERATUR

BRYANT B I 1932 Hypothyreoidismus in der Otolaryngologie *Mschr Ohrenheilk 66* 387

— 1936 Hypothyroidism in the practice of otorhinolaryngology *Ann Otol* 45 10..

HUTTLROTH R., 1947 *Hormonwirkungen auf die Nase* Leipzig

KRAJINA Z., 1961 Rhinitis vasomotoria *Rad Jugoslavensko Akademije Zagreb* 3.. ...

LASKIEWICZ A 1951 Changes in the upper respiratory organs and the ear in the underlying disfunction of the thyroid gland (hypothyreosis) *Acta Otolaryng (Stockh)* 39 188

PROETZ A W., 194. The thyroid and the nose *Ann Otol* 6 328

PROUD G O and LANGE R D., 1957 The effect of the thyroidectomy on the nasal mucosa of experimental animals *Laryngoscope 67* 201

WALSH TH 1950 Vasomotor rhinitis *Laryngoscope 60* 360

Prof Dr B Gušić Mažuranic 39 Zagreb
Jugoslawien

DISCUSSION

G Kelemen K weist auf Veränderungen der Schleimhaut der oberen Luftwege hin die Honor B Fell (Cambridge) durch abgestufte Dosierung von Vitamin A hervorrufen konnte



Fig. 1. Muqueuse de la *corde vocale de l'Homme* : vue générale de la corde vocale, dégageant l'épithélium et le chorion. On voit dans la partie profonde du chorion des fibres nerveuses amyéliniques, dont quelques unes sont plus fortement imprégnées du colorant.

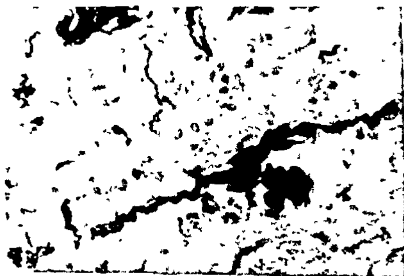


Fig. 2. Vues à un plus fort grossissement, on distingue bien ces fibres nerveuses amyéliniques, dont certaines, plus importantes, sont groupées en faisceaux parallèles et sinueux. Voici en haut et à gauche *une fibre isolée*. *Dans la* partie inférieure de la coupe on voit des fibres nerveuses amyéliniques au contact d'un vaisseau.

Il est regrettable, que dans la plupart des travaux consacrés à la neuro physiologie de la phonation, on s'intéresse d'une façon presque exclusive au muscle vocal seul, en négligeant systématiquement l'étude histologique de la muqueuse de la corde. Or, cette muqueuse existe, il s'agit d'une membrane parfaitement vivante qui recouvre, et même interpénètre le muscle. Elle comprend un épithélium, un chorion ainsi que des formations fonctionellement très importantes.

Avec notre collègue, le Professeur Agrégé Maillet, nous avons entrepris des recherches sur l'innervation de la corde vocale, en dirigeant plus spécialement nos investigations sur les terminaisons neuro végétatives au niveau des divers éléments fonctionnels de la muqueuse cordale.

MATÉRIEL ET MÉTHODE

Matériel

Nous avons utilisé comme objet de recherche la corde vocale de l'homme prélevée après laryngectomie totale et nous avons soigneusement limité notre étude aux éléments exempts de tout processeus néoplasique.

Nous avons également pratiqué des recherches analogues sur le chien et sur le chat, mais le résultat de ces travaux nous a paru trop insuffisant pour que nous puissions en faire état dans cette communication.

Technique

La technique utilisée a été celle de Champy-Maillet, au tétraoxyde d'osmium iodure de zinc. Il s'agit d'un procédé de coloration-fixation, qui possède une sorte de spécificité à l'égard des fibres amyéliniques du système neuro-végétatif, et qui permet en particulier la coloration de l'axoplasme des cellules nerveuses et de leur prolongement, alors que les autres techniques (argent par exemple) sont des méthodes neuro fibrillaires qui peuvent également imprégner le réticulum (ce qui peut engendrer des confusions avec la coloration des fibres conjonctives).

RÉSULTATS

Un premier point paraît se dégager de cette étude, c'est l'importance de l'appareil glandulaire et vasculaire, ainsi que de l'innervation qui s'y rapporte.

Un deuxième point semble intéressant: il s'agit de la présence de cellules de Langhans évoluant au voisinage de fibres nerveuses intra et sous épithéliales.

Dispositions générales des fibres nerveuses amyéliniques

Sur une vue générale topographique de la corde vocale humaine (Fig. 1) on voit bien la disposition d'ensemble de la majeure partie des fibres du système neuro végétatif.

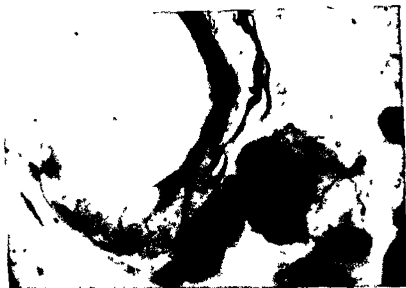


Fig. 4. *Coupe d'un canal excréteur.* On voit ici la section du canal excréteur de glandes choriales dont la paroi est bordée puis pénétrée par des fibres nerveuses amyeliniques.

Ces relations sont intimes, et nous avons pu observer des terminaisons de fibres amyéliniques se plaçant en contact direct avec la glande après avoir traversé la membrane basale (Fig. 3).

Dans plusieurs cas il nous a été permis de constater l'importance de l'innervation réservée au canal excréteur de ces glandes choriales. Sur la

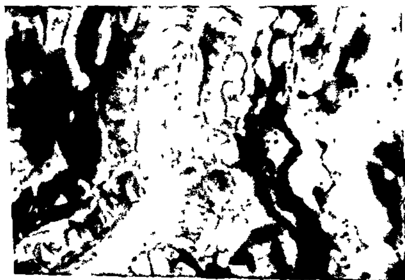


Fig. 5. Artère sectionnée au moment de sa bifurcation. On peut se rendre compte de l'importance de l'innervation de cette artère par le nombre de fibres amyéliniques qui cheminent le long de ses parois.



Fig. 3. — A un plus fort grossissement, on se rend compte de la façon intime dont les cellules glandulaires sont, en quelque sorte, pénétrées par les terminaisons des fibres nerveuses amyéliniques. Voici un groupe de 3 glandes coiffées par des éléments neuro-végétatifs qui se terminent en contact intime avec les cellules épithélio-glandulaires après avoir traversé la basale.

Celles-ci évoluent surtout dans la partie profonde du chorion (fibres intra-choriales). Cependant il existe également des fibres nerveuses intra-épithéliales et sous épithéliales.

D'une façon générale les fibres intra-choriales se réunissent sous la forme d'un faisceau irrégulier composé d'éléments entrecroisés (Fig. 2). Elles se détachent des divers *éléments du chorion où elles apparaissent* diversement intéressées par leur section.

Elles présentent un trajet généralement sinueux et parfois spiralé.

Relations neurofonctionnelles

Il est intéressant de noter comment s'effectuent les relations terminales de contact entre l'appareil nerveux d'une part, et d'autre part le système fonctionnel glandulaire et vasculaire.

a) Glandes

Contrairement à l'opinion habituellement répandue *les glandes de la muqueuse vocale* sont importantes. Nous avons pu intéresser dans nos coupes de nombreuses formations acineuses, en pleine activité fonctionnelle.

L'intérêt de la méthode de Champy-Maillet est de bien mettre en évidence les rapports existants entre les fibres nerveuses amyéliniques et les cellules épithélioglandulaires.



FIG. 7. Figure axée sur la ligne de démarcation épithélio-choriale. On voit bien ici de nombreuses cellules de Langhans sous épithéliales qui se situent au voisinage d'un véritable réseau sous épithélial de fibres nerveuses amyéliniques.

fulement les cellules de Langhans plus ou moins volumineuses et fortement colorées, mais dont les prolongements rameux souvent très épais se différencient du trajet *finement monoliforme* des fibres nerveuses amyéliniques.

A ce sujet les cellules de Langhans n'occupent pas toujours la même situation par rapport à la membrane basale de l'épithélium muqueux. Elles sont tantôt sus-épithéliales et tantôt sous épithéliales (Fig. 7). Leur intérêt réside également dans les rapports possibles existant entre les cellules de Langhans et les terminaisons intra épithéliales des fibres nerveuses amyéliniques.

Les plaques motrices terminales et les fuseaux musculaires

Bien que notre travail ait été orienté vers l'étude des fonctions neuro-végétatives de la muqueuse cordale, nous avons recherché la présence des fuseaux neuromusculaires.



Fig. 6. Fibre nerveuse amyélinique intra-épithéliale pénétrant profondément dans les assises de l'épithélium. Elle semble provenir d'un réseau sous-épithélial en contact avec les cellules de Langhans.

Fig. 4 on peut suivre le trajet d'un véritable fuseau de fibres nerveuses amyéliniques placées au contact du canal excréteur, mettant ainsi en évidence tout l'intérêt fonctionnel du système glandulaire annexé à la muqueuse de la corde vocale.

b) *Vaisseaux*

De son côté *l'appareil vasculaire* reçoit un important contingent de fibres nerveuses amyéliniques. Et ceci doit être souligné étant donné le rôle majeur joué par la régulation de la circulation sanguine à l'intérieur même de la corde vocale.

La Fig. 5 concerne une artériole sectionnée probablement au moment de sa bifurcation et dont les parois sont bordées par un très important fuseau de fibres nerveuses amyéliniques.

Fibres nerveuses intra-épithéliales et sous-épithéliales

Dans de nombreuses coupes nous avons pu observer des fibres nerveuses amyéliniques cheminant profondément dans les divers assises de l'épithélium de la muqueuse cordale. Il s'agit de *fibres intra-épithéliales* (Fig. 6).

L'intérêt de ces fibres est qu'elles semblent se détacher *d'un réseau de fibres sous-épithéliales* au milieu desquelles évoluent des cellules de Langhans.

Là encore, nous devons noter l'avantage de la méthode d'imprégnation de Champy-Maillet. Cette technique nous permet en effet de distinguer par-

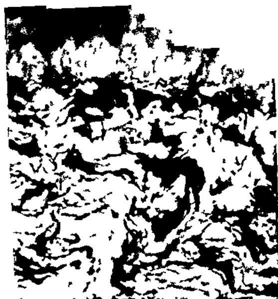


Fig. [illegible] — Figure axée sur la ligne de démarcation épithélio-chordale. On voit bien ici de nombreuses cellules de Langhans sous-épithéliales qui se situent au voisinage d'un véritable réseau sous-épithélial de fibres nerveuses amyéliniques.

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La encore, nous devons noter l'avantage de la méthode d'imprégnation de Champy-Maillet. Cette technique nous permet en effet de distinguer par-

jonctive nous nous rangeons plus volontiers à l'avis de Pierre Masson qui envisageait pour ces cellules une *origine neuro-ectodermique*.

Cette hypothèse pourrait permettre d'expliquer les relations paraissant exister entre les cellules de Langhans et les fibres nerveuses intra-épithéliales.

Il n'est pas impossible en effet de supposer que ces cellules sécrètent un ferment jouant un rôle dans l'activité métabolique de la muqueuse cordale.

Quoi qu'il en soit, et dans le cadre du travail préliminaire que nous venons de présenter, il semble logique d'admettre une activité fonctionnelle non négligeable de la part de *la muqueuse de la corde vocale* qui, grâce à sa *fonction glandulaire*, grâce à sa participation active à la *régulation sanguine* et *enfin grâce à l'action sécrétoire probablement enzymatique* de ses cellules de Langhans, mériterait la faveur d'une promotion dans l'étude neurophysiologique du mécanisme de l'émission vocale. Il est probable que la clé de ce problème se trouve dans de nouvelles recherches histochimiques et histo-enzymologiques.

SUMMARY

The authors experimenting on the larynx of man and other mammals, describe the endings of amyelinic nervous fibres observed in the muscle and in the mucous membrane of the vocal chord.

ZUSAMMENFASSUNG

Aufgrund experimenteller Untersuchungen an Kehlkopfen des Menschen und bei verschiedenen Saugetieren beschreiben die Verfasser die marklosen Nervenfaserenden, die sie in dem Stimmbandmuskel und in der Schleimhaut der Stimmbänder beobachtet haben.

49 Bd Béranger, Tours, France



Fig 8 *Muscle vocal de l'Homme* (thyro aryténoïde interne) On aperçoit clairement sur cette coupe l'image classique des plaques nerveuses motrices terminales

Nous devons avouer que nous ne les avons pas trouvées, soit qu'ils ne fussent pas présents dans notre matériel, soit que notre technique ne corresponde pas exactement à de pareilles recherches

Toutefois nous avons pu déceler les images caractéristiques des plaques motrices terminales classiques (Fig 8)

CONCLUSIONS

Il semble qu'en ce qui concerne l'innervation neuro-végétative de la muqueuse de la corde vocale, on se trouve en présence de trois dispositions différentes des fibres nerveuses amyéliniques

— des fibres choriales profondes
— des fibres intra-épithéliales
— et enfin, des fibres immédiatement sous-épithéliales cheminant parallèlement à la membrane basale de l'épithélium

Les fibres choriales profondes innervent l'appareil glandulaire et les vaisseaux Quant aux fibres intra-épithéliales et sous épithéliales, il semble que leur présence soit liée à l'activité des cellules de Langhans

L'origine de ces cellules est assez mal connue elle est même discutée Morphologiquement, il s'agit de cellules volumineuses à prolongement rameux et généralement épais et fortement colorées par le réactif Il est possible mais cela n'est pas prouvé qu'on se trouve en présence de cellules pigmentaires pouvant être assimilées aux mélanoblastes de l'épiderme Considérées par certains auteurs comme étant d'origine *mésodermique et con-*

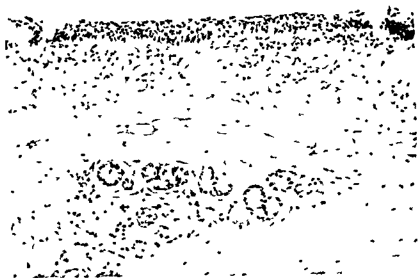


Abb. 1. Übergangsepithel. S. I. ♀ 85jähr., Trachea inf., 6 Tage post tracheot.

stellt. Die Gruppe V umfasst naturgemäss ausschliesslich Laryngektomierte. Wir entnahmen bei der Sektion Material für die histologische Präparation an homologen Stellen des Tracheobronchialbaumes, d. h. a) unterhalb des Tracheostoma, b) auf Bifurkationshöhe, c) im re. und d) im li. Hauptbronchus. Neben den üblichen Färbungen, Hämalaun-Eosin, van Gie-

TABELLE 1. *Status post tracheotomiam*

Gruppe groupe group	Tracheotomia — exitus Tage jours days	Nr. Pat. (total = 21)	Aetas Jahre, années, years	Indicatio operationis
I	2–4	3: 2 ♂ 1 ♀	17–67	Tu. cerebri Poliomyelitis Contusio cerebri
II	6–8	4: 2 ♂ 2 ♀	53–85	Tu. laryngis inop. 2 Contusio cerebri Haemorrhagia cerebri
III	14–16	4: 2 ♂ 2 ♀	57–65	Tu. laryngis inop. 2 Tu. cerebri Trauma laryngis (suicid.)
IV	21–35	3: 2 ♂ 1 ♀	25–76	Tu. laryngis laryngekt. 2 Insufficientia cordis
V	[illegible]–3 Jahre	7: 7 ♂	[illegible]	Tu. laryngis laryngekt.

DIE HISTOLOGIE DER TRACHEOBRONCHIALSCHLEIMHAUT BEIM TRACHEOTOMIERTEN[1]

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Durch histologische Untersuchungen mit Spezialfärbung, Auszählung von Schleimdrüsenzellen und vergleichende Messungen der Schleimhautdicke wird die Reaktion der Tracheo-Bronchialschleimhaut auf die Tracheotomie im frühen und späten postoperativen Verlauf untersucht. Die Veränderungen am Epithel im Sinne von Metaplasien und an den Drüsen (mucipare Hyperplasie) erreichen ihr Maximum in der zweiten postoperativen Woche und bilden sich in der Folge zum Teil wieder zurück.

Mannigfache Indikationen gaben in den vergangenen 10–20 Jahre in vermehrtem Masse Anlass zur Vornahme einer Tracheotomie. Dieser Eingriff stellt ein recht erhebliches lokales Trauma dar. Vor allem wird eine durchgehende Hals-Trachealwandverletzung gesetzt, ein Fremdkörper in Form der Kanüle wird eingeführt und in situ gehalten, und die Wunde wird einer p. s.-Heilung überlassen. Diese operativen Veränderungen ziehen naturgemäss die Tracheo-Bronchialschleimhaut im Operationsgebiet und bis weit in die Peripherie der Atemwege in Mitleidenschaft. Wenn die primären akut entzündlichen Erscheinungen einmal abgeklungen sind, persistiert ein unphysiologischer Belüftungszustand, der durch Austrocknung und Abkühlung auf den feingeweblichen Aspekt der tieferen Atemwege des Kanülen- bzw. Stomaatmers einwirkt. Dies haben bereits Aboulker u. Schwaab dargelegt. Man gewinnt nun allerdings anhand des klinischen Erscheinungsbildes den Eindruck, dass sich Trachea und Bronchien dieser Patienten mit der Zeit an die neuen Belüftungsverhältnisse adaptieren. Dieser Umstand veranlasste uns, die histologischen Tracheo-Bronchialwandveränderungen in Relation zur Dauer des kanülierten Zustandes zu studieren.

Unser Sektionsgut umfasst 22 Operierte und 5 normale Vergleichsfälle. Wir haben, wie aus Tab. 1 ersichtlich ist, die ersteren nach dem Kriterium der Dauer des kanülierten bzw. laryngektomierten Zustandes vom Eingriff bis zum Exitus in 5 Gruppen eingeteilt. Hier sind auch das Alter der Patienten und die klinischen Indikationen zur Tracheotomie zusammenge-

[1] Mit freundlicher Unterstützung der Stiftung für wissenschaftliche Forschung an der Universität Zürich.

Herr Prof. Dr. L. Uehlinger, Direktor des Pathologisch-Anatomischen Institutes der Universität Zürich hat uns liebenswürdigerweise das Untersuchungsmaterial überlassen. Frau A. Hirs besorgte die histologische Bearbeitung und Herr A. Häberli die photographischen Aufnahmen. Den beiden Mitarbeitern sei hiermit aufs beste gedankt.

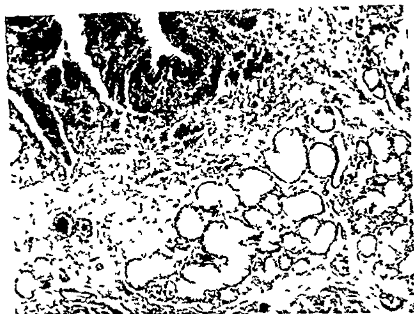


Abb. 3. Hypertrophie und Schleimanschoppung in den Trachealdrüsen. H. K. 8, 26jähr., Tracheo sup., 7 Tage post tracheot.

zilientragend, aber sehr häufig finden wir es ersetzt durch ein Übergangsepithel von unterschiedlicher Schichtdicke (Abb. 1). Die Submucosa ist wechselnd infiltriert und ihre Gefässe sind stark dilatiert.

Erosive Wandveränderungen beobachten wir auch noch im Anfang der dritten Woche. In diesem Zeitpunkt dominiert aber ein typisches geschichtetes Plattenepithel. Dieses wird bekanntlich beim Normalen im Bereich der Pars membranacea der Bifurkationsgegend als Metaplasie häufig angetroffen. Wir finden es in unseren Präparaten nicht selten *am Übergang* der *Pars membranacea* zur Pars cartilaginea, vielleicht als Ausdruck einer vermehrten mechanischen Belastung dieser Gegend. Es zeigte sich oft ohne ersichtlichen Grund, gelegentlich aber auch besonders über Tumorzell*nestern auffallend papillär angeordnet* (Abb. 2). *Zylinderepithel ist in den Schnitten jeden Stadiums* vorhanden, sei es im Sinne von Restinseln *oder* als Regenerat. So liegen oft mannigfaltig geartete und geschichtete Epithelformen nebeneinander. Besonders von der vierten Woche an nimmt die Zylinderepithelauskleidung wieder an Ausdehnung *zu und* weist auch zahlreiche Becherzellen *auf*. In der Umgebung der Drüsenausführungsgänge, wo hier die Regeneration erfolgen dürfte, sitzt häufig Zylinderepithel. Es wäre allerdings auch denkbar, dass hier die Nachbarschaft zur Schleimdrüse eine bessere Befeuchtung gewährleistet und das Zylinderepithel resistenter sein lässt.

Aus der klinischen Erfahrung kennen wir die verschiedenen Arten von Sekretionsstörungen, die im Gefolge einer Tracheotomie auftreten können



Abb. 2. Pflasterepithel über Tumorzellnestern. B. J. ♂, 56jähr., Trachea sup., 6 Mte post tracheot.

son, Elastin wurden solche mit PAS angestellt, um die schleimbildende Aktivität der Drüsen erfassen zu können.

Die Schwierigkeit der Beurteilung der Präparate liegt in der Inhomogenität unseres Krankengutes. Alter, Geschlecht, Grundkrankheit, vorbestehende, insbesondere entzündliche Bronchialaffektionen liessen sich nicht miterfassen. Die normalerweise bestehenden geringfügigen Unterschiede zwischen Trachealwand und Bronchialwand mussten ebenfalls vernachlässigt werden, da eine grössere Zahl von normalen Vergleichsfällen fehlte. Trotz dieser Unzulänglichkeiten gewinnt man den Eindruck einer gewissen *Einheitlichkeit der Reaktions-, Heilungs- und Adaptationsvorgänge*, die anhand einiger Beispiele besprochen werden sollen.

Im Verlauf der ersten 8 Tage (Gruppen I & II) überwiegen akut entzündliche Vorgänge. Die aufgelockerte Epithelschicht ging oft bei der Materialentnahme verloren. Wir finden aber fibrinös belegte, mit Erythrozyten und Entzündungszellen durchsetzte Erosionsflächen. Das mehrreihige oberflächliche Zylinderepithel ist noch stellenweise erkennbar, zum Teil gar

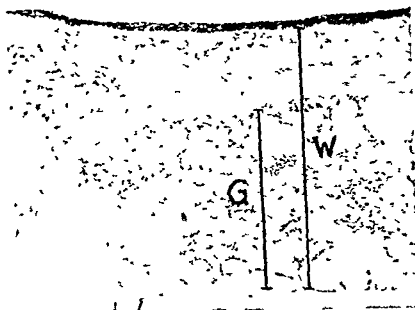


Abb a Clar Lt Wall Rati 0 69 V W 8 66jahr re Hauptbronchus, 2 1/2 Mte post tracheot

ausgezahlt und die Resultate Abb 4 zusammengestellt Eine Zunahme der absoluten Zahl von Druseneinheiten um beinahe das Doppelte im Verlauf der ersten 4 Wochen ist erkennbar Gleichzeitig vermehren sich die PAS positiven schleimbildenden Elemente absolut und prozentual

Spater d h im Zeitabschnitt von 2 1/2 Monaten bis zu 3 Jahren post Tracheotomiam zeichnet sich wiederum eine rucklaufige Tendenz ab Vago hat von einer metaplasia mucipara, d h einer Umwandlung von serosen in mucinose Druseelemente gesprochen Diese Erscheinung konnte allerdings auf einer Tauschung beruhen da die prall gefullten schleimbildenden Adenomere die serosen Adenomere verdrangen Unseres Erachtens ist die Annahme berechtigt dass der chronische entzundliche Reiz der direkten Trachealatmung mit der sie begleitenden Austrocknung neben der Hypertrophie auch eine Hyperplasie der Schleimdrusen zur Folge hat (Reid 1960 Restrepo & Heard 1963)

Reid hat als Kriterium fur die histologische Diagnose einer chronischen Bronchitis den sog Gland to Wall Ratio angegeben Die Relation der Dicke der Schleimdrusen zur Dicke der submukosen Schleimhautschicht zwischen Lamina propria und Perichondrium des Knorpels (Abb 5) ergibt einen Faktor der nicht grosser als 0 25 sein soll Unsere nicht tracheotomierten erwartungsgemass normalen Vergleichsfalle ergeben einen Wert von 0 28 Bei unseren Trachealatmern ubersteigt dieser Wert den Grenzwert Reids von 0 36 und erreicht im Verlauf von 2 Wochen 0 39 und 0,41 In der dritten und vierten Woche nimmt er wiederum ab (Abb 6) Die Drusenschicht bleibt dabei ziemlich konstant gegenuber der Norm aber deutlich verdickt,

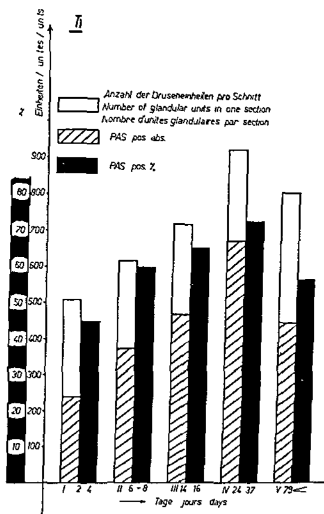


Abb. 4. Tracheobronchialdrüsen

Es ist nicht möglich, die hämorrhagisch-fibrinöse bzw. trockene Form der Tracheitis post tracheotomiam von der hypersekretorischen tracheo-bronchorrhoischen Form histologisch zu differenzieren. Fraglos bestimmen verschiedene Faktoren, wie zentrale Regulationsstörungen, Störungen des Wasser-Elektrolythaushaltes, die mikrobielle Besiedlung, unsachgemässe Kanülenpflege und Traumatisierung etc. die Manifestationsform der Tracheo-Bronchitis. Im histologischen Präparat lassen sich oft Schleimanschoppungen in den Drüsengängen erkennen, die an Mucoviscidosis oder eine Dyskinesie in der Ausstossung des Sekretes erinnern (Abb. 3). Die Ductus sind hier erweitert, sodass es zu dem den Bronchologen bekannten röntgenologischen Bild der „franges“ kommen konnte (Israels & Mitarb. 1955, Stutz & Vieten, 1955). Eine Gesetzmässigkeit des Verhaltens der Drüsen ist aber noch viel weniger fassbar als beim Epithel. Möglicherweise wird das Bild auch unter pathologischen Verhältnissen durch den phasisch ablaufenden Sekretionsvorgang im Bereich einzelner Wandpartien des Atemtraktes verwischt. Die serösen und die mucinösen Drüsenanteile lassen sich aufgrund von Spezialfärbungen mit PAS gut differenzieren. Wir haben sie

otomy. The findings of an increased glandular mucous activity and of squamous metaplasia are related to the length of time post-tracheotomy with the most pronounced changes observed during the 2nd postoperative week. These changes tend to revert partially toward a more normal state during the following weeks.

RÉSUMÉ

Étude de la réaction de la muqueuse trachéo-bronchique à la trachéotomie par l'examen histologique de l'épithélium, par l'étude du nombre de cellules glandulaires de la sousmuqueuse et par des mesures comparatives de l'épaisseur de la muqueuse. Les arbres trachéo-bronchiques ont été obtenus par autopsie à divers moments de l'évolution postopératoire. On voit ainsi que les altérations épithéliales et glandulaires passent par un maximum au cours de la 2ème semaine pour diminuer ensuite.

LITERATUR

Au[illegible] R. P., Lissac, J. u. d Saint Paul, O., 19[illegible]: *Le laryngologiste et le donnée actuelle [illegible] ment des in[illegible]ffrances respiratoires*. Librairie Arnette, Paris.

Israëls, A. A., Orie, N. G. M., Geelen, J. F. M., Wabbinga, R. J. und Huizinga, E., 19[illegible]5: La bronchographie dans l'asthme. *Bronches* [illegible] 11–31.

Otto, H., 19[illegible]7: Die Bewertung des metaplastischen Bronchialepithelregenerates. *Beitr. Path. Anat.* 117 39[illegible]-424.

Otto, H. und Wagner, H., 19[illegible]6: Beitrag zur Frage der Regeneration des Bronchialepithels. *Beitr. Path. Anat.* 116 436–460.

Reid, L., 1960: Measurements of the bronchial mucosa gland layer. A diagnostic yardstick in chronic bronchitis. *Thorax* 1[illegible] 132-141.

Restrepo, G. und Heard, B. E., 1963: The size of the bronchial glands in chronic bronchitis. *J. Path. Bact.* 8[illegible] 38[illegible].

Schwab, W., 19[illegible]: Über morphologische und funktionelle Veränderungen am Atmungstrakt nach Laryngektomie. *Arch. Ohr. Nas. Kehlkopfheilk.* 166 444–47[illegible].

Stutz, E. und Vieten, H., 19[illegible]: *Die Bronchographie*. Thieme Verlag, Stuttgart.

Vaco, A., 19[illegible]7: La sindrome secretiva in [illegible] grande sindrome bronchiale. *Soc. It. Laryng. Otol. Rinol. Atti del X[illegible] Congr.*

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DISCUSSION

G. Kelemen: Untersuchung der Hautauskleidung der antethorakalen Röhre (Oesophagusplastik nach F. von Bakay) zeigte eine Umwandlung, die diese Haut einer funktionierender Mucosa näher brachte.

C. C. Ormerod: F. C. Ormerod was interested to listen to Dr. von Schulthess and to see his sections of tracheo-bronchial mucous membrane with the metaplastic changes from columnar ciliated to squamous epithelium. Some thirty years ago he made many histological examinations of tracheo-bronchial mucosa as diagnostic measures for carcinoma of the bronchus. It was not an uncommon occurrence to find metaplasia similar to that shown by Dr. von Schulthess, sometimes there was a carcinoma in the columnar epithelium, sometimes in the squamous, and in others there was no carcinoma. It had not been realized then what part excessive cigarette smoking played in the occurrence of carcinoma. It

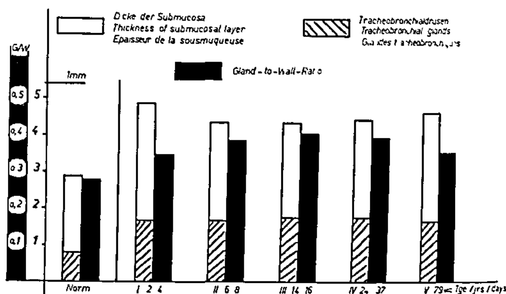


Abb. 6. Messung der Tracheobronchialschleimhaut

während die gesamte Wanddicke durchwegs erheblich vermehrt ist. Ziemlich parallel der numerischen Zunahme der PAS-positiven Elemente vergrössert sich also auch der Gland-to-Wall-Ratio bis zur 3. Woche, um später wieder abzunehmen. Das entzündliche Ödem dürfte diese Messergebnisse nicht unerheblich beeinflussen.

Der frühe und späte postoperative Verlauf nach Tracheotomie lässt nach dem Gesagten eine gewisse Gesetzmässigkeit im Ablauf der Heilungs- und Adaptationsvorgänge in der Schleimhaut der tieferen Luftwege erkennen. Das Frühstadium zeigt die Kriterien der akuten zum Teil erosiven Tracheobronchitis mit Umwandlung des Zylinderepithels in Übergangs- und Pflasterepithel. Im Verlauf von 3–4 Wochen, vermutlich abhängig von äusseren Faktoren, Kanülenreiz, Tracheo-Bronchialpflege, Befeuchtung, klingen diese Erscheinungen ab und das histologische Bild tendiert wieder zur Normalisierung (vgl. Tierversuche Otto). Eine gewisse Fibrose der Submucosa oder entzündliche Restinfiltrate könnten auf Grund der Beurteilung einzelner Präparate für die Beibehaltung des Pflasterepithels an gewissen exstomanahen Bezirken verantwortlich sein. Die unverkennbare Vermehrung des mukösen Drüsenanteils mit späteren Anzeichen von Regression ist ein Kriterium zur Beurteilung der schleimbildenden Aktivität der Glandulae tracheo-bronchiales. Es sollte die frühzeitige Wiederherstellung eines intakten Zylinderepithels angestrebt werden, damit der physiologische „mucous blanket", der „tapis roulant" der Tracheobronchialauskleidung wieder normal funktioniert. Alle Massnahmen, die diese Wiederherstellung fördern, sollen bei der Pflege des Tracheotomierten berücksichtigt werden.

SUMMARY

Histological examination of trachea and bronchi including glandular cell counts and measurements of mucosal thickness have been performed following tracheo-

MECHANICAL CO-FACTORS IN OLFACTORY STIMULATION

E. Bocca, A. R. Antonelli and O. Mosciaro
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From the E.N.T. Clinic of the University of Sassari

The importance of mechanical stimulation of the olfactory epithelium as a co-factor in the odorous sensation, which had been previously demonstrated by us in animals, has been confirmed in the course of the present investigation on human subjects. It appears that mechanical stimulation makes odorous perception possible even for subliminal concentrations of the odorous substance in the mucus and that, on the contrary, in the absence of a mechanical stimulus, no odorous sensation arises however high the concentration may be.

It has been repeatedly observed in the course of the last ten years that the stimulation of the olfactory epithelium of cats or rabbits by a flow of inert gas may elicit an elective electrical response at the level of the olfactory bulb, as well as of the higher stations of the olfactory pathway and of the olfactory cortex. The observation has been further confirmed by the recent electrophysiological investigation in cats by Antonelli & Pignataro (1962).

That a mechanical stimulus may induce an activity in the olfactory cells is also believable on an anatomical basis because it is a general property of cilia-bearing structures that they behave as mechano-receptors. However, it is very difficult to establish which one might be the real sense of these mechanically induced responses as we have no proofs whatsoever that such responses have a psychological correlate. At this point, we should recall, on the one hand, the statement of Proetz, the father of modern rhinology, when he says that in the absence of an air current, if the nasal cavities are filled with odorous solutions, there is a stimulation of tactile sense but olfaction does not occur. On the other hand we should recall the recent experiences by Ueki & Domino (1961), who demonstrated that the threshold for an odorous substance is lowered by the insufflation of an inert gas into the olfactory fissure.

A more complete experimental evidence of the fact was afforded by the excellent investigations of Antonelli (1962) and *Tedini* (1961) who recorded potentials from the olfactory bulb and olfactory centers of cats following mechanical stimulation of the olfactory epithelium, alone or associated with simultaneous intracarotidal injection of a solution of an odorous substance.

As a result of their experiments, the following conclusions were drawn

is possible that the metaplastic changes observed were due to the effects of smoking He asked if Dr von Schulthess was aware of the smoking history of the tracheotomized patients he described A tracheostomy naturally led to mucosal changes in the lower respiratory tracts but the changes might have already been produced by smoking

I Zollner Die interessanten Beobachtungen des Kollegen Schulthess an der Trachealschleimhaut interessieren mich besonders in ihrer Analogie zum Mittelohr Die Zunahme der Schleimdrusen in den ersten Wochen nach Tracheotomie konnte man als eine zweckmassige Reaktion ansehen Bemerkenswert ist die Beobachtung ihrer Ruckbildung die wir leider im Mittelohr kaum erreichen konnen Die Neigung zur Metaplasie des Bronchialepithels zu Plattenepithel ist bekannt, eine Ruckbildung von echtem Plattenepithel zu Zylinderepithel wie sie, soweit ich verstand, bei dem letzten Fall angenommen wurde widerspricht allen bisherigen Beobachtungen

A Eckert Mobius Zu den Diskussionsbemerkungen von Herrn Zollner ist zu bemerken, dass sich das Plattenepithel der ausseren Haut offenbar anders verhalt als das der Schleimhaut Die Schleimhaut ist omnipotent und kann je nach den ausseren Bedingungen die bei ihr wirksam werden, Platten oder Flimmerepithel bilden Das zeigt sich am offensichtlichsten in der Nase, die bei extremer Weite und dadurch bedingter Austrocknung (Ozaena) ihr Flimmerepithel durch Plattenepithel ersetzt und bei operativer Verengerung der Nase infolge der dadurch veranderten Feuchtigkeits und Ernahrungsbedingungen erneut Flimmerepithel entstehen lasst

G von Schulthess (Schlusswort)

zu *J C Ormerod* The state of the respiratory tract of our patients previous to tracheotomy is unknown Thus we cannot exclude previous changes in the slides What we know from clinical experience is that patients with chronic bronchitis react with a stronger inflammation to tracheotomy

zu *F Zollner* Die metaplastischen Vorgange in der Tracheo Bronchialschleimhaut wurden vor allem durch Otto studiert Es steht fest dass Pflasterepithel nur durch Regeneration von Zylinderepithel ersetzt werden kann wahrend Ubergange von Zylinderepithel in Ubergangsepithel beobachtet werden konnen In Trachea und Bronchien besteht die Tendenz das zur primaren Abheilung der Lasion rasch produzierte Pflasterepithel wieder durch Zylinderepithel zu ersetzen so dass eine Restitutio ad integrum moglich ist

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eliciting an olfactory sensation and the flow of air simply recruits more odorous substance from the adjoining mucous surfaces. This first hypothesis must be discarded on the basis of the experiments of Proetz which were previously quoted, of those of Fortunato & Niccolini (1958) showing that the odorous flow must impinge upon the olfactory neuroepithelium with "a certain force" to enable an olfactory perception to take place. Finally, there is the proof that a "recruiting" air flow is much less effective than a flow localized to the olfactory fissure only.

2. A mechanical stimulation of the olfactory epithelium must be present at the same time as the specific odorous stimulation if the odour is to be perceived. This second view seems to be more correct inasmuch as all experimental evidence favours it.

The cross evaluation of the data obtained from human and animal experiments seems to fall out from the realm of possibilities the hypothesis of a hematogenous olfaction by direct stimulation of the rhinencephalum in the sense of Marco Gimenez & Morera (1954) as well as that of an hematogenous olfaction through the liberation of the injected odorous solution into the nasal mucus in the sense of Bartalena (1957) and Simeria (1957). Without an air flow, no olfaction is present, regardless of the way by which the odorous substance reaches the nasal cavities.

The fact that even a minor mechanical stimulation of the olfactory epithelium may bring about an olfactory sensation for a blood borne odorous solution accounts for the reason why a theory of a direct stimulation of the olfactory centers by an odour containing blood current could be postulated.

RESUME

Des expérimentations conduites sur l'homme ont permis de confirmer les résultats de nos recherches précédentes sur l'animal en démontrant que la stimulation mécanique de l'épithèle olfactif est un co-facteur essentiel de la perception olfactive. La stimulation mécanique permet la perception des odeurs même lors que la concentration de la substance odoreuse dans le mucus est au-dessous du seuil; d'autre part en défaut de stimulation mécanique, la sensation odoreuse demeure constamment absente si haute que la concentration soit. De ces observations on peut tirer des conclusions intéressantes à propos de la nommée olfaction hématogène.

ZUSAMMENFASSUNG

Die Wichtigkeit des mechanischen Reizes des Riechepithels als Kofaktor der Geruchssensation wurde von uns bereits am Tier festgestellt und konnte mit dieser Untersuchung für den Menschen bestätigt werden. Es scheint, als ob der mechanische Reiz zu einer Geruchsempfindung auch bei unterschwelliger Konzentration der Geruchssubstanz im Mukus führt und dass es dagegen unabhängig von der Konzentration zu keiner Geruchssensation kommt, wenn der mechanische Reiz fehlt. Diese Beobachtungen führen zu einigen wichtigen Schlüssen über das lang umstrittene Problem der sogenannten hämatogenen Olfaktion.

1. The olfactory bulb responds to the mechanical stimulation of the olfactory cells by a flow of inert gas.

2. No electrical activity is aroused in the olfactory bulb or centers by the intracarotidal injection of odorous substance in the tracheotomised animal

3. If during the intraarterial injection, a flow of inert gas is directed towards the olfactory fissure with a velocity of 0 5–1 liter per minute, a distinct response is elicited on the side of the injection

4. If the flow of gas is not directed towards the olfactory fissure a response is present only for far greater flow rates.

5. In the animal with spontaneous respiration less evident responses have been observed after the intravenous injection of an odorous solution, which were synchronous with the acts of respiration.

6 No rhinencephalic response was traceable after surface anesthesia of the olfactory mucous membrane or after the section of the olfactory peduncle.

Therefore, it may be argued that the mechanical stimulation of the olfactory cells may allow the perception of subliminal concentrations of an odorous substance, such as may be present in the mucus of the olfactory region following capillary diffusion after an intraarterial injection of the substance itself. A sort of summation should take place at the level of the olfactory bulb following this threshold stimulation: an anatomical support to this view may well be given by the big convergence of neurons in the olfactory glomeruli, each glomerulus receiving the afference of thousands of sensory cells

The point was now to establish if something analoguous to what was observed in the animal was also observable in man For this purpose, ten normal subjects of a young age, capable of keeping an apnea of at least 1 min duration, received an intravenous injection into a cubital vein, of about 1 cc of a solution of an odorous substance (essence of citral or peppermint) prepared according to a standardized formula During and after the injection no olfactory sensation was perceived as long as the subject was in apnea As soon as normal respiration began again, odour perception started, in accordance with the data of previous investigators (Teatini & Pinetti, 1961) On the other hand, if during the injection, the subject being in apnea, a flow of pure nitrogen at the velocity of 0 5/1 liter per minute was blasted into the olfactory fissure by means of a specially devised polyethylene tube, a specific odorous perception arose, with a latency of 12–13 sec from the beginning of the injection, which represents the arm-to-nose circulation time If the flow from the tube was directed into the nose, but outside the olfactory area, much greater flow rates were necessary in order to evoke the sensation (6 to 10 liters per minute)

As a consequence of these observations two alternative hypotheses are possible

1 The concentration of the odorous substance being eliminated in the nasal mucus of the olfactory fissure does not reach the threshold for

only those individuals could be used in whom the superior turbinals had been removed by surgery or disease. He asked if Professor Bocca had any experience of subjective sensations of smell being caused by mechanical stimulation of the olfactory epithelium—*or of the nerve endings*.

F. Zöllner: Wenn das Vortragsthema dabei auch nur am Rande berührt wird, so möchte ich doch eine praktisch interessante Beobachtung erwähnen. Eine schwere, ½ Jahr anhaltende Parosmie, die auf vorübergehendes Abschwellen der Riechspalte nicht reagierte, kam nach operativer Erweiterung rasch zum Schwinden. Die elektronenmikroskopische Untersuchung durch Frau D. Molkert ergab Fibrillenbildung zwischen Epithelzellen und Degeneration einzelner Zellen.

I. Bocca (Reply): 1. To *van Dishoeck* I am able to reply that the persistence of an olfactory response to intravenous ether in tracheotomized subjects might *well be due to a higher diffusibility of this substance*, which might cause a higher concentration of the substance in the mucus; nevertheless, this is not a counter-proof to the fact that an air current is necessary to evoke the sensation; on the contrary, it may well be that the slightest movement of air in the nasal cavities such as is normally present in a tracheotomized patient during swallowing, moving the cheek muscles, and also during the breathing acts, may be sufficient to attain the olfactory threshold when the mucus concentration of the odorous substance is greater, such as it is with ether.

2. To *Ormerod* I should like to reply that an odorous sensation could never be evoked *in man by mechanical stimulation alone of the olfactory cleft*.

3. I quite agree with *Zöllner* that the cases he observed of post-infectious parosmia may be of a central origin. By way of analogy his observations lead me to think that some case of post-infectious anosmia may be due exclusively to a loss or a degeneration of the olfactory cilia and not to a complete degeneration of the olfactory cells.

REFERENCES

ANTONELLI A R 1962 Elektrophysiologische Untersuchungen am Olf Iti nsss tem d r Katze w ihrend intrahimatischer Injektion von Essenzlosungen Z Laryng Rh n l Otol 41 822 828

ANTONELLI A R and PENATARO O., 1962 Risposta elettrica del preparato medioj nt no pretrigeminale di gatto a stimoli di lunga durat i prima e dopo lesioni rinencefal ch Arch Ital Otol 73 646 652

BARTALENA G F., and VAGLINI I 1957 Rilievi sulle variazioni del radicale If c a o nel muco nasale conseguenti all olf izione ematogena Boll Mal Orecch 6 ... (19

FORTUNATO V., and NICCOLINI P 1958 « L olfatto cognizioni antiche e recenti » C llana Scient I I I Rome

MARCO J C GIMENEZ J and MORERA N 1954 La olfacion en los laringect mizad s Rev Esp Otoneurooftal 13 380

PROETZ A W 1953 Essays on the applied physiology of the nose Ann Publ C St Louis

SEMERIA C 1957 La sensazione olfattiva ematogena Arch Ital Otol Suppl 30 (1 9–78

TLATINI G P 1961 Analisi elettrofisiologica del sistema olfattivo del gatto durante la iniezione intraematica di soluzioni di essenze odorose Atti 49° Congr S c Ital O R L Turin 1961

TRATINI G P and PINCINI G 1961 Estimulacion olf toria per via hematica Acta Oto rinolaring Iber Amer 12 417–431

UEKI S and DOMINO E F 1961 Some evidence for a mechanical recept r in olfactory function J Neurophysiol 24 12

The E N T Clinic of the University of Sassari Viale Mancini Italy

DISCUSSION

H A E van Dishoeck An intravenously injected aqueous solution of camphor will not diffuse in the olfactory cleft The camphor will be excreted in the lungs and reach the olfactory cleft only on expiration For this reason as long as the breath is held or in laryngectomized patients no camphor sensation will occur However with ether injected intravenously a distinct ether sensation occurs also in laryngectomized patients That means that the volatile ether diffuses into the olfactory cleft in a sufficient concentration

Air currents are indeed necessary to provoke and intensify olfaction For that reason while sniffing the odorous molecules are concentrated on the olfactory cells According to Amoore in this way the 5 kinds of holes of different proportions are filled with the fitting molecules Even laryngectomized patients know how to produce air currents in their nose and enjoy smoking and eating

I C Ormerod I C Ormerod recalled that Lord Adrian had demonstrated varying action currents in the olfactory nerve of rabbits by applying different olfactory substances to the olfactory membrane Ormerod had made some investigations with Professor Le Gros Clark of Oxford by directing a very fine current of air onto the olfactory epithelium in human subjects It was hoped to produce subjective sensations of different smells by applying this air current to different parts of the olfactory area No sensations of any smells at all were obtained This might have been due to the fact that none of these noses were normal It is impossible to see the olfactory epithelium in a normal human nose and so

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REFERENCES

ANTONELLI, A. R., 1962: Elektrophysiologische Untersuchungen am Olf. kliomssystem der Katze während intrahämatischer Injektion von Essenzlösungen. *Z. Laryng. Rhinol. Otol.* 41, 822-828.

ANTONELLI, A. R. and PICNATARO, O., 1962: Risposta elettrica del preparato mcho... pretrigeminale di gatto a stimoli di lunga durata prima e dopo lesioni rinencefaliche. *Arch. Ital. Otol.* 73, 646-652.

BARTALENA, G. L., and VACLINI, E., 1957: Rilievi sulle variazioni del radicale ... nel muco nasale conseguenti all'olfazione ematogena. *Boll. Mal. Orecch.* 6, ...

FORTUNATO, V. and NICCOLINI, P., 1958: « L'olfatto: cognizioni antiche e recenti ». C. Ita. Scient. I. I. I. Rome.

MARCO, J. C., GIMENEZ, J. and MORERA, N., 1954: La olfacion en los laringectomizados. *Rev. Esp. Otoneurooftal.* 13, 380.

PROETZ, A. W., 1953: Essays on the applied physiology of the nose. Ann. Publ. C. St. Louis.

SEMERIA, C., 1957: La sensazione olfattiva ematogena. *Arch. Ital. Otol.* Suppl. 30, 68, 9-78.

TEATINI, G. P., 1961: Analisi elettrofisiologica del sistema olfattivo del gatto durante la iniezione intraematica di soluzioni di essenze odorose. Atti 49° Congr. Soc. Ital. O.R.L. Turin, 197.

TEATINI, G. P. and PINCINI, G., 1961: Estimulación olfatoria por vía hemática. *Acta Otorinolaring. Iber. Amer.* 12, 417-431.

UETE, S. and DOMINO, E. F., 1961: Some evidence for a mechanical receptor in olfactory function. *J. Neurophysiol.* 24, 12.

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Details die Pathophysiologie des Phänomens der Calciphylaxie betreffend verweisen wir auf eine umfassende Monographie von Selye (1962).

Selye hat bei seinen Versuchen die „auslösenden Substanzen" entweder subcutan, intravenös, intraarteriell oder intraperitoneal appliziert. In unserer Versuchsanordnung wurden die einzelnen Agenzien mittels Aerosolen zugeführt, wobei wir diese Applikationsart aus zweierlei Gründen wählten: Einmal ergibt sich dadurch ein unmittelbarer Kontakt zwischen „auslösender Substanz" und Respirationsschleimhaut, andererseits kommen die meisten dieser Substanzen auch in den Industrieabgasen von Grossstädten vor, so dass die Aerosol-Versuchsanordnung den natürlichen Verhältnissen sehr nahe kommt.

Mit unseren Untersuchungen wollten wir einerseits die Frage klären, ob mit der unterschiedlichen Applikationsart der Aerosolinhalation ähnliche calciphylaktische Reaktionen an der Respirationsschleimhaut auslösbar sind, wie sie Selye nach parenteraler Verabreichung der auslösenden Substanzen in dieser und in anderen Organen erzeugen konnte. Im Falle dies möglich wäre, sollten andererseits die reaktiven Veränderungen studiert werden, die dadurch in der Schleimhaut verursacht werden. In einer Versuchsgruppe haben wir die Aerosolinhalation mit einem *konditionierenden Adjuvans* kombiniert (Eisendextran i.v. vor der Inhalation), das nach Selye zu einer wesentlichen Verstärkung der calciphylaktischen Reaktion führt.

Versuchsanordnung

[illegible] weibliche Albinoratten mit einem durchschnittlichen Körpergewicht von 100 g wurden in 12 Gruppen unterteilt und wie in Tabelle 1 dargestellt, behandelt.

TABELLE 1

Gruppe	Zahl der Tiere	Behandlung: Substanz	%	Aerosoldauer (min)
1		DHT $FeSO_4(NH_4)_2SO_4$	[illegible]	15
[illegible]		DHT $FeCl_2$	[illegible]	15
[illegible]		DHT $FeCl_3$	[illegible]	[illegible]
[illegible]		DHT $FeSO_4$	[illegible]	[illegible]
		DHT $CeCl_3$	1	15
		DHT $KMnO_4$	2	[illegible]
		DHT Ferrivein (Engl. i.v.) $KMnO_4$	2	15
8	[illegible]	DHT $CdCl_2$	[illegible]	[illegible]
[illegible]	[illegible]	DHT $ZnSO_4$	[illegible]	10
[illegible]	5	DHT $CrCl_3$	[illegible]	10
[illegible]	5	DHT Serotonin	1,5	15
[illegible]	5	DHT (Kontrolle)		

DIE EXPERIMENTELLE ANWENDUNG DES PHÄNOMENS DER CALCIPHYLAXIE AN DER RESPIRATIONSSCHLEIMHAUT

K. Burian und F. Frank
Wien, Österreich

Aus der Filialstation der II. Universitätsklinik für Hals-Nasen-Ohrenkrankheiten (Dir.: Prof. Dr. O. Novotny), Wien

Mittels der calciphylaktischen Reaktion ist es im Tierversuch möglich, durch verschiedene, aerogen zugeführte Metallsalze Verkalkungen an der Respirationsschleimhaut und dem Lungenparenchym auszulösen. $KMnO_4$ und $CeCl_3$ erwiesen sich dabei am wirkungsvollsten. Das Ausmass der Verkalkung geht mit den durch das Aerosol bedingten Schleimhautschädigungen nicht parallel. Stärkere Schädigungen oder entzündliche Reaktionen vermindern sogar die Verkalkung weitgehend. Die möglichen Zusammenhänge dieser Versuchsergebnisse mit verschiedenen Berufserkrankungen werden erörtert.

Vor einigen Jahren hat Selye and Hand umfangreicher tierexperimenteller Untersuchungen ein Phänomen beschrieben, das er als „Calciphylaxie" bezeichnet hat. Wir haben die experimentelle Anwendung dieses Phänomens zur Bearbeitung verschiedener oto-rhino-laryngologischer Probleme herangezogen und darüber auf der heurigen Drei-Länder-Tagung in Ravenna berichtet. Am diesjährigen Internationalen Kongress für Bronchologie haben wir unsere Untersuchungen über die experimentelle Verkalkung der Trachealwand mitgeteilt (Burian & Frank, 1964) und in unserem heutigen Referat wollen wir Ihnen über die Auslösung dieses *Phänomens* auf aerogenem Wege und dessen Auswirkungen an der Respirationsschleimhaut berichten.

Unter Calciphylaxie versteht man eine Veränderung der Reaktionslage des Organismus ähnlich einer Überempfindlichkeit, die durch Vorbehandlung mit kalkfreisetzenden Substanzen (beispielsweise Nebenschilddrüsenhormon, Vitamin D, Dihydrotachysterol u. a. m.) hervorgerufen wird und in deren Verlaufe innerhalb einer gewissen „kritischen Periode" die Nachbehandlung *mit „auslösenden Substanzen" zu einer intensiven* Kalkablagerung in den behandelten Geweben führt. Als „auslösende Substanzen" fungieren eine Reihe von Metallsalzen, Eiklar oder Eidotter, aber auch physikalische Reize wie Ausreissen von Haaren oder Zwicken der Haut. Je nachdem, ob diese Stoffe subcutan oder intravenös verabreicht werden, entwickelt sich eine lokale und umschriebene oder eine, dem injizierten Gefässbereich entsprechende, allgemeine Verkalkung. Bezüglich weiterer

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Selye hat bei seinen Versuchen die „auslösenden Substanzen" entweder subcutan, intravenös, intraarteriell oder intraperitoneal appliziert. In unserer Versuchsanordnung wurden die einzelnen Agenzien mittels Aerosolen zugeführt, wobei wir diese Applikationsart aus zweierlei Gründen wählten: Einmal ergibt sich dadurch ein unmittelbarer Kontakt zwischen „auslösender Substanz" und Respirationsschleimhaut, andererseits kommen die meisten dieser Substanzen auch in den Industrieabgasen von Grossstädten vor, so dass die Aerosol-Versuchsanordnung den natürlichen Verhältnissen sehr nahe kommt.

Mit unseren Untersuchungen wollten wir einerseits die Frage klären, ob mit der unterschiedlichen Applikationsart der Aerosolinhalation ähnliche calciphylaktische Reaktionen an der Respirationsschleimhaut auslösbar sind, wie sie Selye nach parenteraler Verabreichung der „auslösenden *Substanzen" in dieser und in anderen Organen erzeugen konnte. Im Falle* dies möglich wäre, sollten andererseits die reaktiven Veränderungen studiert werden, die dadurch in der Schleimhaut verursacht werden. In einer Versuchsgruppe haben wir die Aerosolinhalation mit einem konditionierenden *Adjuvans kombiniert* (Eisendextran i. v. vor der Inhalation), das nach Selye zu einer wesentlichen Verstärkung der calciphylaktischen Reaktion führt.

Versuchsanordnung

65 weibliche Albinoratten mit einem durchschnittlichen Körpergewicht von 100 g wurden in 12 Gruppen unterteilt und wie in Tabelle 1 dargestellt, behandelt.

TABELLE 1

Gruppe	Zahl der Tiere	Behandlung: Substanz	%	Aerosoldauer (min)
1	5	DHT + $FeSO_4(NH_4)_2SO_4$	5	15
2		DHT + $FeCl_2$	5	[illegible]
3	5	DHT + $FeCl_3$	5	15
4		DHT + $FeSO_4$	5	15
5	5	DHT + $CeCl_3$	1	15
6	5	DHT + $KMnO_4$	[illegible]	15
7	5	DHT + Ferrivenin (1 mg i. v.) + $KMnO_4$	2	15
8	10	DHT + $CdCl_2$	1	15
9	5	DHT + $ZnSO_4$	5	[illegible]
10	5	DHT + $CrCl_3$	1	10
11	5	DHT + Serotonin	[illegible]	10
12	5	DHT (Kontrolle)		15

Dihydrotachysterol (Calcamin-Wander) wurde zu Versuchsbeginn in den Magen instilliert (1 mg/ml), 24 Stunden später, — das entspricht bei den angewandten Substanzen, der für die Auslösung einer calciphylaktischen Reaktion „kritischen Periode", — wurde die Aerosolinhalation verabreicht. Wir verwendeten dafür ein für klinische Zwecke übliches Aerosolgerät, das eine Partikelgrösse von 1–3 μ erzeugt. Dieses Aerosol wurde an zwei diametral entgegengesetzten Stellen in einen Glaskäfig geleitet, um eine möglichst gleichmässige Verteilung des Aerosols innerhalb des Käfigs zu gewährleisten. Als Agenzien haben wir verschiedene Metallsalze und Serotonin verwendet, die sich nach den Erfahrungen von Selye bei parenteraler Applikation als sehr wirksame Verkalkungsstoffe erwiesen.

Während des Versuches erhielten die Tiere Trockenfutter und Wasser als Trinkflüssigkeit. 6–8 Tage nach der Aerosolinhalation erfolgte die Tötung und Entnahme der Lunge, Trachea und des vorderen Anteils des Septums nasi zur histologischen Untersuchung. Zur Färbung wurde die Technik nach von Kossa, van Gieson und MacManus angewandt.

Ergebnisse

Die Verträglichkeit der verwendeten Aerosole erwies sich als unterschiedlich. Während die Tiere der meisten Versuchsgruppen die Inhalation gut vertrugen, ergaben sich nach Anwendung von $CdCl_2$ und $CrCl_3$ grosse Ausfälle. Im Verlaufe der Cadmium-Inhalation zeigten die Tiere dieser Gruppe noch keine auffallenden Besonderheiten, 1–2 Tage danach ging jedoch annähernd die Hälfte davon zugrunde, wobei pneumonische Veränderungen als Todesursache im Vordergrund standen. Wie aus Tabelle 2 zu entnehmen, fanden sich an der Schleimhaut des Nasenseptums und der Trachea nur minimale Kalkeinlagerungen und das pneumonisch veränderte Lungenparenchym war überhaupt frei davon.

TABELLE 2

Substanz	Verträglichkeit	Ausmass der Kalkablagerung
DHT + $FeSo_4(NH_4)_2So_4$	gut	+ −
DHT + $FeCl_2$	sehr gut	0
DHT + $FeCl_3$	sehr gut	+
DHT + $FeSo_4$	sehr gut	+
DHT + $CeCl_3$	gut	+
DHT + $KMnO_4$	gut	
DHT + Ferrivenin + $KMnO_4$	gut	+
DHT + $CdCl_2$	schlecht	−
DHT + $ZnSo_4$	gut	+ −
DHT + $CrCl_3$	sehr schlecht	nicht ausgewertet
DHT + Serotonin	gut	0
DHT	—	0



Abb. 1. Massive Kalkeinlagerung in der Lamina propria einer Nasenmuschel nach DHT und $CaCl_2$. Nr. 5. Färbung nach v. Kossa. Vergr. 160×

Chromchlorid erwies sich schon während der Inhalation als sehr toxisch, so dass die Tiere dieser Gruppe entweder während der Behandlung oder kurz danach zugrunde gingen und daher histologisch nicht ausgewertet werden konnten.

Die Tiere der Kontrollgruppe Nr. 12, die nur mit DHT allein behandelt wurden, zeigten keinerlei Veränderungen der Schleimhaut im Sinne einer Calciphylaxie. Ebenso erwiesen sich alle Metallsalze, wenn sie ohne DHT-Vorbehandlung angewandt wurden, als effektlos; wir haben daher darauf verzichtet, die Kontrollgruppen gesondert anzuführen. Trotzdem sei diese Beobachtung unterstrichen, zumal es sich bei $CaCl_2$, $CeCl_3$ und $KMnO_4$ um sogenannte „direkte Verkalkungsstoffe" handelt, mit denen Selye auch *ohne DHT-Sensibilisierung allein* durch die subcutane Applikation *Verkalkungen des Gewebes* erzielen konnte. Allerdings musste man, um Vergleiche ziehen zu können, die verabreichten Dosierungen berücksichtigen, die *bei der Aerosolapplikation* naturgemäss wesentlich *geringer als bei subcutaner Injektion* sind. In diesem Zusammenhang sei auf eine vorangegangene Arbeit (Burian & Frank 1961) sowie auf den Abschnitt „Direct Calcifiers" bei Selye (1962) verwiesen.

Die Auswertung unserer histologischen Untersuchungen haben wir in Tabelle 2 zusammengefasst. Darin wird das Ausmass der Kalkablagerung in der Schleimhaut bzw. dem Lungenparenchym mit den Bezeichnungen (0), (±), (+), (++), (+++) charakterisiert. Dabei bedeutet (+ –) umschriebene und zarte Kalkablagerungen, die innerhalb der Versuchsgruppe nur bei einzelnen Tieren beobachtet werden konnten. (+ bis +++) bezeichnet die Kalkablagerung mengen- und ausdehnungsmässig, wobei unter (+++) entweder massive umschriebene oder sehr ausgedehnte, jedoch feingranulierte Kalkablagerungen zu verstehen sind.

Die histologische Untersuchung ergibt uns ferner eine gewisse Überein-

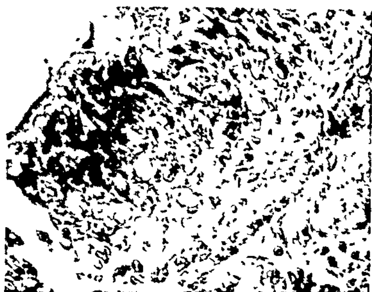


Abb. 2. Einlagerung zarter Kalkgranula im Epithel, in einigen oberflächlich liegenden Epithelzellen besonders koncentriert. Färbung nach v. Kossa. Vergr. 800×

stimmung der Befunde, als calciphylaktische Veränderungen in der Lunge meistens auch mit solchen in der Trachealschleimhaut verbunden sind. Hingegen müssen dabei nicht immer auch Kalkablagerungen in der Septumschleimhaut nachweisbar sein. Umgekehrt weisen Tiere, die Verkalkungen in der Septumschleimhaut zeigen, immer auch solche in der Trachea und Lunge auf.

Der in der Schleimhaut eingelagerte Kalk wird in der Färbung nach von Kossa als distinkte Schwärzung nachgewiesen. Bei sehr massiven Kalkeinlagerungen kann Kalk beim Schneiden des Präparates herausbröckeln, so dass er nicht immer genau in der Ebene des histologischen Schnittes zu



Abb. 3. Kalkeinlagerung entlang der bindegewebigen Drüsenkapseln. Färbung nach v. Kossa. Vergr. 800×

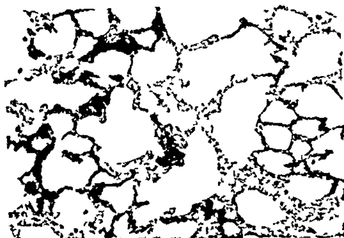


Abb. 4. Übersichtsbild des Lungenparenchyms mit Kalkeinlagerung in den Alveolarsepten (DHT und $KMnO_4$-Aerosol). Färbung nach v. Kossa. Vergr. 160×

liegen kommt und daher bei der photographischen Reproduktion mitunter unscharf erscheint.

Die Kalkablagerung kann unterschiedlich erfolgen. Meistens lagern sich die Kalksalze entlang kollagener Fasern ab und führen zu einer förmlichen Inkrustierung derselben (Abb. 1). Eine andere Art der Kalkablagerung, die besonders bei Anwendung von $KMnO_4$ erfolgt, ist in Form zarter schwarzer Granula in den Gefäßwandungen, Bindegewebsfasern, aber auch den Drüsenzellen und Drüsenausführungsgängen sowie im Plasma und den Kernen der Epithelzellen (Abb. 2, 3). In der Lunge wird Kalk in den Alveolarsepten sowie in der Schleimhaut der Bronchien und Bronchioli (Abb. 4, 5) abgelagert.

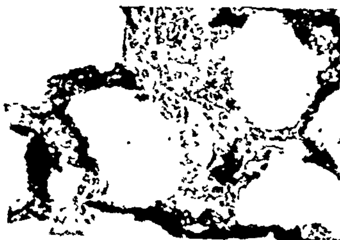


Abb. 5. Detailbild aus Abb. 4. Vergr. 500×



Abb. 6. Ausgedehnte Kalkeinlagerung in der Bronchialwand, stellenweise auch in den Alveolarsepten (DHT und $KMnO_4$ Aerosol). Färbung nach v. Kossa. Vergr. 80×

In Versuchsgruppe 7 haben wir ähnlich wie dies auch Selye in seinen Versuchen getan hat, $KMnO_4$ mit der zusätzlichen intravenösen Applikation eines Adjuvans (Eisenzucker) kombiniert. Eine sehr dichte und wesentlich intensivere Kalkablagerung als im Kontrollversuch Nr. 6 war die Folge (Abb. 7). Damit konnte die Calciphylaxie-fördernde Wirkung von Eisenverbindungen auch bei Aerosolapplikation der „auslösenden Substanz" erwiesen werden.

Vergleicht man verschieden lange überlebende Tiere, so gewinnt man den Eindruck, dass der in der Schleimhaut eingelagerte Kalk mit zunehmender Überlebenszeit eine Verschiebung erfährt. Bei Tieren, die 6 Tage nach der



Abb. 7. [illegible] intensive Verkalkung des Trachealepithels nach DHT, Ferrivenin und $KMnO_4$ Aerosol. Schwere Schädigung des Epithels mit stellenweiser Regeneration eines Plattenepithels. Färbung nach v. Kossa. Vergr. 400×

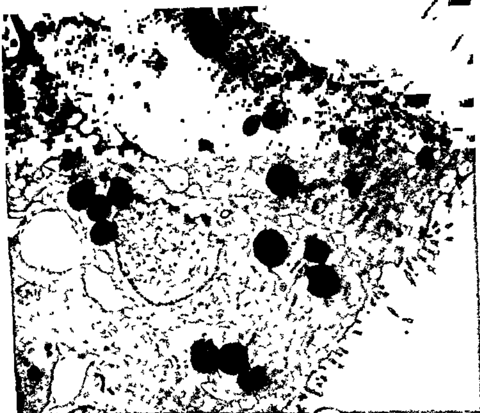


Abb. 8. Reichlich elektronendichte Massen in regenerierten und noch undifferenzierten hochprismatischen Epithelzellen, die vermutlich Kalk entsprechen. Vergr. 8000×

Inhalation getötet wurden, sind die Kalkgranula vorwiegend in den Drüsenzellen, den Ausführungsgängen, der Basalmembran und geringgradig auch in den basal liegenden Epithelzellen nachzuweisen. Bereits zwei Tage später sind auch die oberflächlich liegenden Epithelzellen mit dichten Kalkgranula erfüllt und an der Epitheloberfläche ist ein schwarzer Saum ausgeschiedener Kalkgranula nachweisbar. Man gewinnt somit den Eindruck, dass der *durch die calciphylaktische Reaktion abgelagerte Kalk sowohl durch* Schleimdrüsen als auch vom Stroma der Lamina propria transepithelial ausgeschieden wird. In Zusammenarbeit mit Stockinger vom Histologischen Institut der Universität Wien haben wir begonnen, die calciphylaktisch veränderte Nasen- und Trachealschleimhaut elektronenmikroskopisch zu untersuchen. Dabei konnten wir im Plasma und den Kernen von Bindegewebs- und Epithelzellen reichlich kugelig konfiguriertes, sehr elektronendichtes Material nachweisen, das wahrscheinlich den schon lichtmikroskopisch beschriebenen Kalkgranula entsprechen dürfte (Abb. 8). Weitere differenzierende Untersuchungen werden zu klären haben, ob es sich bei diesen elektronenmikroskopischen Befunden tatsächlich um Kalk handelt,



Abb. 6. Ausgedehnte Kalkeinlagerung in der Bronchialwand, stellenweise auch in den Alveolarsepten (DHT und $KMnO_4$-Aerosol). Färbung nach v. Kossa. Vergr. 80×

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Abb. 7. B[illegible]der intensive Verkalkung des Trachealepithels nach DHT, Ferrivenin und $KMnO_4$-Aerosol. Schwere Schädigung des Epithels mit stellenweiser Regeneration eines Plattenepithels. Färbung nach v. Kossa. Vergr. 400×

(1962) unter der Bezeichnung „Siderocalciphylaxie" bei parenteraler Anwendung der auslösenden Substanz schon beschrieben hat.

$ZnSO_4$ zeigt nur eine mässige Wirksamkeit und diese auch nicht bei allen Versuchstieren.

$CrCl_3$ *konnte* wegen der grossen Ausfälle nicht beurteilt werden. Aus anderen Versuchen wissen wir jedoch, dass es bei intravenöser Anwendung von $CrCl_3$ bei DHT-vorbehandelten Tieren zu sehr massiven Verkalkungen im Herzen und der Trachealschleimhaut kommt.

Ein interessantes Problem stellt die Frage dar, was in weiterer Folge mit dem im Gewebe eingelagerten Kalk geschieht und welche Reaktionen er als Fremdkörper in der Schleimhaut auslöst. Unsere diesbezüglichen Untersuchungen sind noch nicht abgeschlossen, es scheint jedoch, dass Bindegewebsproliferation, Fibrose und Atrophie der Schleimdrüsen die weiteren Konsequenzen darstellen.

Fragt man sich, ob die von uns erhobenen Befunde irgendwelche Rückschlüsse auf die Humanpathologie erlauben, so sind zwei Umstände zu berücksichtigen. Einmal kommen eine grosse Zahl der von Selye als „auslösende Substanzen" beschriebenen Agentien in den Industrieabgasen vor (Cr, Mn, Fe, Zn, Cd usw.). Die Luft, in der wir leben, ist ein Aerosol, dessen disperse Phase die erwähnten Metallsalze in Form flüssiger oder fester Partikelchen enthält. Was die in unserer Versuchsanordnung gewählte Vorbehandlung mit DHT betrifft, so ist zu bedenken, dass es sich dabei um einen Eingriff in den Kalkstoffwechsel handelt, der zu ähnlichen Veränderungen führt, wie er beim Menschen nicht nur durch endokrine Störungen der Nebenschilddrüse, sondern auch durch Vitamin-D-Intoxikation, Nierenfunktionsstörungen und Darmresorptionsstörungen verursacht werden kann.

Somit bestehen theoretisch unter besonderen Umständen auch für den Menschen Voraussetzungen, die unserer Versuchsanordnung ähnlich sind. In diesem Zusammenhang sei auf jene der Gewerbemedizin hinlänglich bekannten pathologischen Veränderungen an der Lunge und der Respirationsschleimhaut verwiesen, die man nach chronischer Mangan-, Chrom- oder Kadmiumvergiftung auf aerogenem Wege beobachtet hat. Sowohl die Kadmiumrhinitis als auch die Alveolarseptenfibrose nach Manganvergiftung sind durch eine diffuse Bindegewebsvermehrung bzw. Atrophie der Schleimhaut charakterisiert. Unsere bereits erwähnten, noch nicht abgeschlossenen Untersuchungen der Folgezustände calciphylaktischer Reaktionen scheinen ebenfalls in Richtung Fibrose und Sklerose zu weisen.

SUMMARY

By means of the calciphylactic reaction and the use of various metallic salts applied aerogenically, *calcification of the respiratory* membrane and of the parenchyma of the lung can be produced. $KMnO_4$ and $CrCl_3$ proved to be most *effective in this connection*. The extent of the calcification does not conform to

wobei wir vielleicht auch nähere Hinweise auf den Sekretionsmechanismus der Respirationsschleimhaut gewinnen werden können.

In den Epithelzellen findet man Kalkgranula sowohl in den Flimmerzellen, als auch in den Becherzellen. In einzelnen Versuchsgruppen gewinnt man zwar den Eindruck, als wären die Flimmerzellen dichter mit Granula erfüllt, woraus sich allerdings keine Rückschlüsse ziehen lassen, da durch die Schleimabstossung der Becherzellen eine raschere Entleerung dieser Zellen möglich ist. Im Vergleich mit den bereits entleerten Becherzellen kann somit der irrtümliche Eindruck erweckt werden, dass die noch erfüllten Flimmerzellen eine grössere Affinität zur Kalkaufnahme besitzen.

Die angewandten Aerosole führen auch zu mehr oder minder starken Schädigungen des Schleimhautepithels, die nur nach $CdCl_2$ tiefgreifender waren. Diese schwereren Schädigungen bedingen jedoch keinesfalls eine Verstärkung der Verkalkung. Wir haben daher darauf verzichtet, auf das Ausmass der Epithelschädigungen näher einzugehen, nachdem kein Parallelismus zwischen Schleimhautschädigung und Grad der Verkalkung besteht.

Besprechung der Ergebnisse

Unsere experimentellen Untersuchungen haben ergeben, dass auch auf aerogenem Wege eine calciphylaktische Reaktion an der Respirationsschleimhaut auslösbar ist. Unter den von uns verwendeten Agentien, die sich bei subcutaner Applikation alle als sehr wirksam erwiesen haben, entfaltete lediglich Serotonin und $FeCl_2$ keine Wirksamkeit. Die anderen verwendeten Eisensalze ($FeSo_4(NH_4)_2So_4$, $FeCl_3$, $FeSo_4$) ergaben nur bei einzelnen Versuchstieren eine schwache calciphylaktische Reaktion. Ebenso erwies sich $CdCl_2$ als nicht sehr wirksam. Es ist jedoch bemerkenswert, dass trotz der schweren pneumonischen Veränderungen und Epithelschädigungen der Respirationsschleimhaut, die durch Cadmiuminhalationen verursacht wurden, keine stärkeren Verkalkungen auftraten. Es ist dies ein Beweis dafür, dass es sich bei der calciphylaktischen Reaktion weniger um eine dystrophische, sondern in weit grösserem Masse um eine metastatische Verkalkung handelt.

Massive, jedoch umschriebene Verkalkungen konnten mit $CeCl_2$ ausgelöst werden, wobei besonders das Lungenparenchym und die Trachealschleimhaut betroffen waren.

Nach $KMnO_4$-Anwendung fanden sich regelmässig bei allen Versuchstieren Kalkeinlagerungen in Form diffus verteilter zarter Granula. Unter dieser Versuchsanordnung glauben wir auch einen gewissen Ausscheidungsmechanismus beobachtet zu haben, der sowohl über die Schleimdrüsen als auch vom Schleimhautstroma in transepithelialer Richtung verläuft und noch eingehenderem Studium unterzogen werden soll. Sehr auffallend ist die deutliche Verstärkung der Verkalkung nach $KMnO_4$-Aerosol bei gleichzeitiger intravenöser Applikation von Eisenzucker, ein Phänomen, das Selye

DEVELOPMENT AND FUNCTION OF THE SPIRAL CANALICULAR SYSTEM

E. BORGHESAN
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From the Oto-Laryngological Clinic of the University of Palermo

The canalicular spiral system derives from the epithelium of the outer spiral sulcus and extends towards the prominence and the spiral ligament. The comparison between the development of the canalicular spiral system and that of other cochlear structures induces the author to confirm what he suggested in 1949 about the secreting modality of the cochlear endolymph.

In the spiral ligament Shambaugh (1909) showed some epithelial structures provided with ducts he considered as glands; according to Iwata (1924) and other authors such structures are formed of contractile or nervous elements while Cimino (1936) though agreeing with Shambaugh about the secreting function of the epithelial formations denies them to contain ducts. In 1949 I was able to confirm the epithelial structures provided with ducts as described by Shambaugh. I did not, however, consider them as glands but as a *sui generis* canalicular system, which together with the stria vascularis and the spiral prominence constitutes an apparatus. The cochlear endolymph derives in my opinion from this apparatus according to the following modality: the stria secretes some elements of the endolymph, the villi of the prominence secrete the plasma of the endolymph itself, the cells of the canalicular system convey it towards the cochlear duct and towards the interstitial spaces of the spiral ligament where I think there is a histologic safety-device reabsorbing a part of the secreted plasma and endolymph in order to make the endolymphatic tension constant.

With the aim to get a deeper knowledge of such an interesting argument, I have studied the development of the spiral canalicular system, comparing it to that of other cochlear structures which as is known develop according to a special chronological order. I made investigations on four-day-old rabbits since at that stage the structures of the cochlear duct are in progressive segmentary development proceeding from the apex towards the vestibulum.

In a cross section of the cochlear duct almost up to the apex, the epithelial formations are represented by a band composed of four segments: in the intercellular spaces of the segment from which will derive the epithelium of the outer spiral sulcus is seen an osmiophilous substance that

the mucous membrane lesions caused by aerosol. More pronounced lesions or inflammatory reactions diminish quite considerably the calcification. The connections which may possibly exist between the results of these animal experiments mentioned above and the occupational diseases are being discussed.

RÉSUMÉ

A l'aide de la réaction calciphylactique et grâce à l'apport aérogène de divers sels métalliques il est possible dans l'expérience sur l'animal de déclencher des infiltrations calcaires dans la muqueuse respiratoire et dans le parenchyme pulmonaire. Sous ce rapport $KMnO_4$ et CeCl se sont montrés les plus efficaces. Le degré d'infiltration calcaire ne va pas de pair avec les lésions de muqueuse causées par l'aérosol. Des lésions plus prononcées ou des réactions inflammatoires amoindrissent même dans une large mesure la dégénérescence calcaire. Les rapports éventuels entre ces résultats d'expérience et diverses maladies professionnelles sont à l'examen.

LITERATUR

BURIAN, K. und FRANK, F. 1964. Experimentelle Untersuchungen zur Sklerosierung der Trachea. Wr. Klin. Wschr. In Druck.

SELYE, H. 1962. Calciphylaxie. The University of Chicago Press.

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DISCUSSION

F. C. Ormerod. Ormerod had seen Dr. Burian's section with great interest and noted the considerable changes in the respiratory epithelium apparently caused by the application of certain chemical substances. He recalled the serious necrotic changes in the nasal mucosa experienced by the early workers in the chromium plating industry—though this might be the direct result of inhaling nitric acid vapour. Another example of noxious effect of chemical substances is seen in the case of the workers in the nickel industry in South Wales, in whom carcinoma of the ethmoid cells is so common as to be accepted as an occupational risk.

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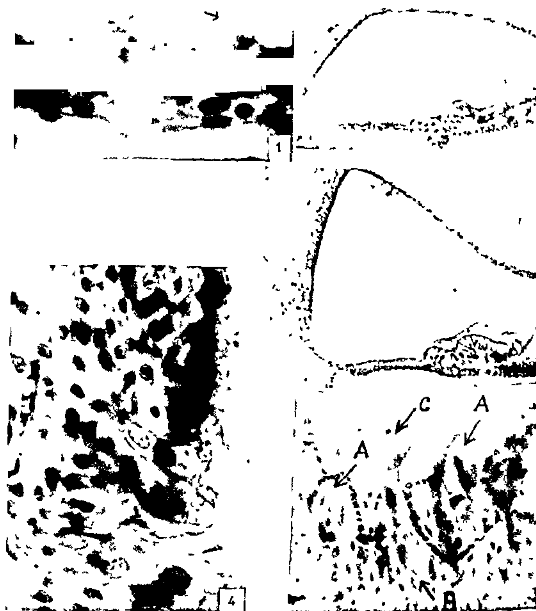
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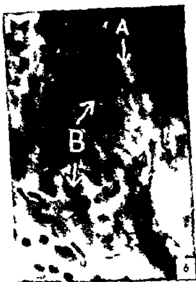
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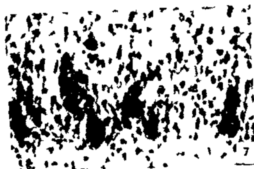


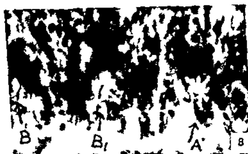
sometimes juts out, like a drop, into the cochlear duct (Fig 1) The grea epithelial ridge has its origin sooner than the differentiation of the org of Corti

In another section of the apical turn (Fig 2) the greater epithelial ri is developed and connected with the limbus and with the organ of Coi the tectorial membrane is delineated, and clearly noticeable are the h cells, Deiters' cells, the tunnel and Nuel's spaces The structures of the ou wall, on the contrary, are not yet greatly differentiated, being the st constituted of a strip of pigmented cells and of non-differentiated cel The canalicular system and the prominence are not yet existing

In the medial turn of the same duct (Fig 3) the greater epithelial rid









remains unchanged Deiters cells are taller the limbus is more developed the spiral prominence is constituted of non differentiated cells and under the pigmented cells of the stria is noticeable a stratum of clear cells rich in vessels From the epithelial cells of the outer spiral sulcus originate epithelial columns, the most precocious of which points towards the prominence (Fig 4) while other columns extend into spiral ligament

At the beginning of the basal turn the limbus has reached its final structure the spiral prominence is organized as a special formation so that in a horizontal section (Fig 5) it appears constituted of a series of clear spaces the one separated from the other by epithelial and connective cells and from the cochlear duct by means of the cells of the outer spiral sulcus (arrow C) These spaces contain fibro-epithelial formations (villi) (arrow A) capillaries and an uncoloured substance The epithelial columns that branch out from the epithelium of the outer spiral sulcus are composed of two segments the outer one (Fig 6 arrows A B) appears as a compact column the inner segment is constituted of clear cells (arrow C) The

structure of the epithelial columns is more evident when these are seen in a frontal section. Figure 7, in fact, shows the cross section of the more peripherical tract of the same columns, which here are formed of compact cellular groups, in the inner tract the cells of these cellular groups are often radially arranged round a thin canal (Fig. 8, arrow A), that gets larger forming more or less evident cavities (Figs. 8–9, arrows B), which may contain very clear epithelial cells (Fig. 8, arrow B). One of these cavities (Fig. 9, arrow A) is separated from the cochlear duct by means of the cells of the outer spiral sulcus.

In a cross section of the cochlear duct, near the end of the basal turn the greater epithelial ridge begins its regressive phase originating therefore in the inner spiral sulcus, the canalicular system appears to be the same as in adult rabbits and the vessels run superficially among the pigmented cells of the stria vascularis.

The histological results point out that in the intercellular spaces of the epithelial stratum of the outer spiral sulcus, as soon as it gets differentiated is found a substance, very likely plasma, which is transferred into the cochlear duct. Later on, from this epithelium derives a *sui generis* structure that is connected with the spiral prominence, the interstitial spaces of the spiral ligament, with the cochlear duct and presents the anatomical conditions apt to transfer fluids, namely, it works as a canalicular system.

The development of the cochlear duct seems to show that this system differentiates later, but matures earlier than the stria, as if the economy of the cochlear duct, in the embryological phase, should need the precocious function of the canalicular system. In order to evaluate the maturation of the stria, Grisanti's opinion has been taken into consideration, according to which the stria can secrete only when its vessels are intimately related to the pigmented cells. I found that such an event occurs when the regression of the greater epithelial ridge begins. The evolution of this last structure is very interesting because it is fully active earlier than that of the other structures (with the exception of the cells of the outer spiral sulcus), and regresses only when the stria has completed its development.

The above-mentioned chain of anatomical events suggests that the papilla spiralis is nourished during its development by the greater epithelial ridge, that when the stria is still inactive, the canalicular system is supposed to perform a humoral function. In my opinion, the functional separation of these two last structures existing in the embryonal life persists after the birth, in consequence I think that the present researches confirm the origin of the cochlear endolymph from an apparatus, about the modality of which I have briefly spoken at the beginning of this work.

RÉSUMÉ

Le système canaliculair spiral dérive de l'épithélium du sillon spiral externe et s'étend vers la proéminence et le ligament spiral. La comparaison entre le développement du susdit système et celui d'autres structures cochléaires porte

l'auteur à *confirmer* l'hypothèse avancée en 1949, concernante la modalité de la sécrétion de l'endolymphe cochléaire

ZUSAMMENFASSUNG

Das kanalförmige Spiralensystem kommt aus dem Epithel des *Sulcus spiralis* externus und reicht bis zur Prominentia und Ligamentum spirale. Der Verfasser hat das Verhältnis erforscht, das zwischen der Entwicklung des kanalförmigen Spiralensystemes und der Entwicklung anderer cochlearen Strukturen besteht. Hieraus zieht der Verfasser den Schluss, dass seine Hypothese von 1949 über die Sekretionsmodalität der Endolymphe cochlearis bestätigt werden kann.

REFERENCES

BORGHESAN, L., 1949. Struttura e vascolarizzazione del ligamento spirale. Ipotesi sulla produzione endolinfatica cocleare. Atti della Clin. O.R.L. di Palermo 2° 171 195
— 1957. Modality of the cochlear humoral circulation. *Laryngoscope* 67: 1266.
CIMINO, A., 1956. Sviluppo del solco spirale esterno e della prominenza spirale nel coniglio. *Boll. Mal. dtte O.R.L.* 74: 360.
v. FIEANDT, H. and SAXÉN, A., 1936. Struktur und Funktion der Region des Sulcus spiralis externus im Innenohr des Menschen und des Hundes. *Z. Anat. Entwicklungsgesch.* *106*: 552.
CHISANTI, G., 1957. Lo sviluppo della stria vascolare nel coniglio. *Minerva Otorinolaryng.* 7: 139.
IWATA, N., 1925. Über das „Wurzelepithel" des ligamentum spirale der Schnecke. *Folia Anat. Jap.* 3: 37-85.
SHAMBAUGH, F. G., 1909. Über Bau und Funktion des Epithels im Sulcus spiralis externus. *Z. Oh. Sr. Nas. Kehlkopfheilk.* 58: 280-287.

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PHYSIOLOGICAL INTERPRETATION OF THE ANATOMY OF THE LABYRINTH

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The structure of the labyrinth demonstrates that the stimulus is a perpendicular pressure and traction on the cuticular membranes, leading, not to a deformation, but to a dislocation between hair cell and its supporting cell, both in the acoustic and in the vestibular part. The mechanism of labyrinthine function is to a great extent in harmony with that of the other senses of orientation and regulation of position

Fig 1 illustrates how an individual, in the normal upright position, endeavours to keep his balance by means of tactile-motor reflexes If he is about to fall forward, his toes and forefeet will receive an upward-directed pressure from the floor. This elicits an oppositely directed pressure which corrects the position At the same time, the heels have been about to lift from the floor, the pressure from the floor has diminished, or has completely ceased This decreasing pressure (or traction) elicits a reaction in the direction of the traction which contributes to the correction

If the individual is about to fall backward, the opposed, corrective reactions occur Only, the pressure from the heels is not so active in the event of a fall backward as the pressure from the forefoot was during the tendency to fall forward And indeed, we are not as exposed to falling backward as forward If we consider the entire sole of the foot as an equilibrium-regulating organ of sense, we find that those parts which are opposed show opposed orientation, opposed reaction, and that the most peripheral parts are most sensitive, and most reactive, i e *dominant*

However, this correction also depends upon the vestibular organ which acts according to exactly the same principles If we let the individual hold in his outstretched, upturned hands, two heavy discs of lead, representing the utricular maculae with their otoliths, we see that during a forward fall the pressure of the "otolith" increases anteriorly and decreases posteriorly, and, as described already elicits posture-correcting reflexes by the increasing pressure upon the anterior, more sensitive part The direction of the motor reactions is still against the pressure or with the (relative) traction Corresponding to the fact that the sensitivity is greater in the more peripheral fingers than in the more central palm, the anterior part of the macula is more sensitive than its posterior part Accordingly, the epithelium is taller and the sensory cells larger in the anterior, dominant than in the posterior, subordinate part of the macula, often separated by an even weaker

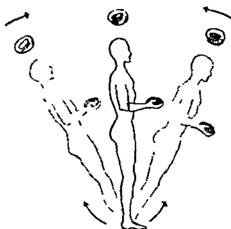


Fig 1

intermediate area which may be completely devoid of sensory cells The laws derived herefrom, viz that the motor reaction is directed against the stimulation in the axis of the stimulated cell, that opposed sides of a sensory organ are of opposed orientation, of opposed reaction, and that the area supplied by the most peripheral part of the distribution of the nerve is dominant are more or less distinctly valid also for the sense of touch, vision and presumably for all posture orienting organs of sense, but nowhere is clearly as in the labyrinth Let me merely show you a single example (Fig 2) from the vestibular labyrinth (the utricular macula of the Echidna)— I have studied the labyrinth of about 40 different species of vertebrates—and let me also remind you of the organ of Corti with its relation between subordinate inner and dominant outer hair cells which



Fig 2 (Anat Inst Groningen)

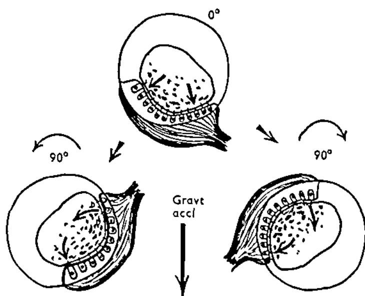


Fig 3

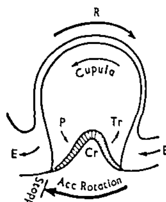


Fig 4

are separated by the blind roof of the tunnel, and of the relation between the number and size of the hair cells in the dominant apex and the subordinate base, corresponding to the course of the nerve

According to these laws, all known vestibular spontaneous, experimental and clinical phenomena become simply explicable This includes also the relation between the effects of ampullopetal and ampullofugal flow in the vertical semicircular canals The fact that as a rule the motor reactions acquire a more or less curved form is in full accordance with these laws, as the total reaction is determined not only by the "front", but also by the dominance of the individual sensory cells and by the degree of curving of the epithelium

The *vestibular tonus reaction* also becomes explicable, if considered as caused by the continuous hydrostatic pressure of the endolymph upon the maculae and crests Apart from the macula lagenae, all vestibular epithelia are facing more or less upward and backward so that the continuous motor reaction against the pressure must be directed upward and backward, well

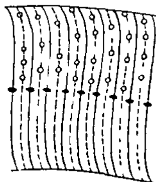


Fig 5

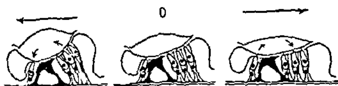


Fig 6

suited to counteract the constant influence of gravity and the tendency to fall forward in walking or jumping If we assume with Breuer and also most recent workers that the otoliths act by sliding and that consequently the sensory cells do not act by pressure but by bending of the sensory hairs one would expect Nature to have placed the sensory epithelia in positions differeng by 90° from their actual positions Regardless from which epithelium the vestibular reaction has been elicited it always comprises the eyes head neck and trunk as well as the limbs The reactions are however easier to observe when they are curved while they are apt to escape detection when rectilinear This is the reason why during a certain period the very slightly curved saccular macula with its very slight differentiation in dominance was believed to have no static function It is also the reason why the progressive reactions were not recognized for such a long time although logically they must correspond exactly to the postural reactions

Let us now consider the functional mechanism e g of the utricular macula in a lateral bent position Corresponding to the course of the nerve the lateral part of the epithelium becomes distinctly dominant You will see (Fig 3) how the pressure on both right parts acts together with the traction on both left parts, which are oppositely oriented inducing a curved ocular deviation to the left directed against the pressure with corresponding reactions of the head trunk, and extremities

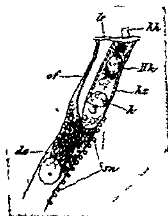


Fig (G Retzius)

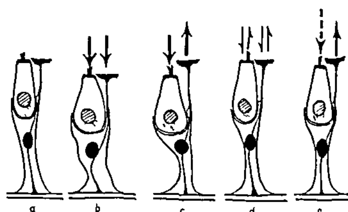


FIG 8

Exactly the same applies to the reactions of the semicircular canals (Fig 4). As a result of a curved acceleration the impact of the endolymph makes the cupula tip around the crest and exert a pressure on one side of it, collaborating with a traction on its oppositely oriented side This elicits a curved motor reaction of the eyes etc, directed against the pressure Accelerations outside the plane of the curvature of each semicircular canal are probably effective too, but to a far lesser degree.

Let us now transfer these vestibular principles to cochlear function Sound waves are, in fact, rapidly and regularly changing, oppositely directed rectilinear accelerations This fits in with the fact that the auditory organs always develop in immediate connection with the saccular macula which by virtue of its structure is particularly susceptible to rectilinear accelerations As in the vestibular organ, the cuticular membranes, owing to their special structure, catch and transmit the physical impact, the corresponding function in the acoustic part must depend upon the tectorial membrane

Under the influence of sound, the tectorial membrane must be assumed to vibrate synchronously with the frequency, taking a radial, slightly S-shaped course, corresponding to the structure of the membrane and the arrangement of the hair cells in rows of the corresponding direction (Fig 5) When moving outward, the elastic membrane becomes flatter and lower,

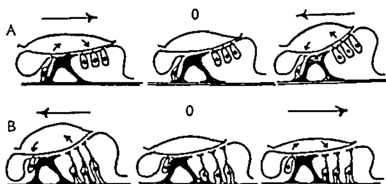


FIG 9



Fig. 10. Vibrational pattern seen from above. O Optimal wave length.

and upon the subsequent inward movement taller and narrower (Fig. 6). The first half of the period, therefore, ought to entail a pressure upon the outer hair cells and a traction upon the inner hair cells, while the latter half of the period entails the opposite effect. At the same time the surface of the organ moves like a see-saw with the fulcrum in the "articulation" between the pillars of Corti, while the Hensen cells like an elastic cushion steady the organ against the tectorial membrane. The spaces of Nuel provide an even distribution of the intracortic pressure.

The mechanism described evidently brings us on to the right track. But it does not explain why each period only gives rise to one and not to two outputs, one for the stimulation of the outer and another for the stimulation of the inner hair cells, as is the case in the lateral line organ (de Vries), nor why each frequency may have its limited range of stimulation. Is there any anatomical element which can help us in this respect?

About a hundred years ago Deiters described the extremely peculiar coupling between each hair cell and its appurtenant Deiters' cell, a phenomenon which is described in every text-book of anatomy, although its physiological significance has entirely escaped attention. The base of each hair cell is depressed and anchored in an "alveolus" at the top of the body of its Deiters cell as already depicted in 1884 by G. Retzius (Fig. 7). The result is that when pressure is exerted in the same phase upon a hair cell and its Deiters' phalangeal head the stiff phalanx pushes the hair cell downwards so that it escapes the influence of the pressure (Fig. 8). It is *only when the two appurtenant types of cell are influenced by opposite phases* that the hair cell is affected, and it is only upon a pressure on the *hair cell* and a diametrically opposed traction on the phalanx that the action will be maximal. This mechanism is supported by the stiffly elastic Retzius fibril in the body of the Deiters cells.

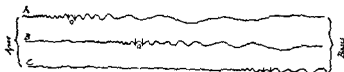


Fig. 11. Vibrational pattern seen from the side. O Optimal wave length. A by low, B medium and C high frequency.

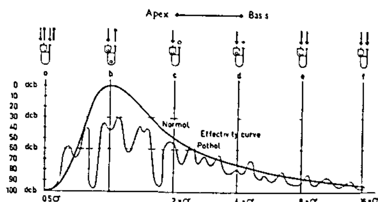


Fig. 12

It must now be assumed that the tectorial membrane vibrates in a way which divides it into opposed phases (Fig. 9 A and B) forming secondary wavelengths in which the wavelength optimal for each individual frequency corresponds to the distance between two radial rows of hair cells, so that the individual row may be exposed to a pressure and the intermediate row of appurtenant phalangeal heads to a traction. We assume that these secondary wavelengths increase in width towards the base and decrease towards the apex (Figs. 10 and 11), so that each frequency has its characteristic wavelength, more or less towards the base for high and towards the apex for deep tones. (There are approx. 3500 rows of hair cells corresponding to the differences in pitch which we are able to perceive.) The possible

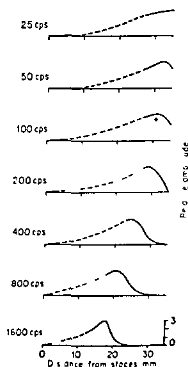


Fig. 13

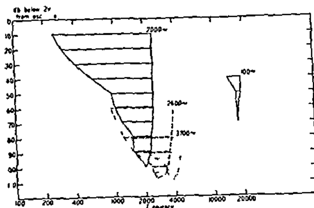


Fig 14

efficiency of the different phases is illustrated in Fig 12 It will be seen that the efficiency curve rapidly declines towards the apex, where the distance of the phases soon *decreases to such an extent that opposed* phases abolish each other, while this distance evenly increases towards the base so that slowly the phase differences become more unfavourable

In order to obtain the named effect, the tectorial membrane apparently has to vibrate according to the improved pattern shown in Fig 9 where A and B signify the two adjacent oppositely vibrating segments of a single secondary optimal wavelength During one half of the period segment A moves outwards The outer hair cells receive a pressure and the inner phalanx a traction *At the same time segment B moves inwards The outer* phalanges receive a traction and the inner hair cell a pressure During the next half period segment A moves inwards The outer hair cells receive a traction, the inner phalanx a pressure, while segment B moves outward so *that the inner hair cell receives a traction and the outer* phalanges a pressure Thus there is only one single stimulation, one output in each period Traction effect on the hair cells is prevented by the way in which hair cells and phalangeal heads are hinged together Fig 12 I have called an 'efficiency or possibility curve', signifying the numerical possibilities caused by the named conditions It would correspond to a stimulation curve if the intensity of the radial vibrations were the same all over, but it is not This may be seen amongst others from v Bekesy's basilar curves (*Fig 11*) and from the distribution of the intensity of the microphonic effect (This effect is presumably due to the movements of the tectorial membrane possibly its impact on the organ of Corti) Presumably, the culmination of intensity coincides approximately with the site of the opti*mum wavelength This will make the stimulation curve* far steeper and narrower and thereby physiologically satisfactory In other words, it presumably coincides with Galambos and Davis' curves representing the frequency range which can stimulate a single nerve fibre (Fig 14)

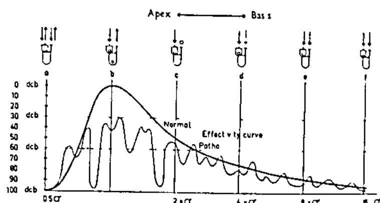


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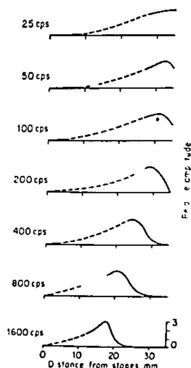


Fig 13

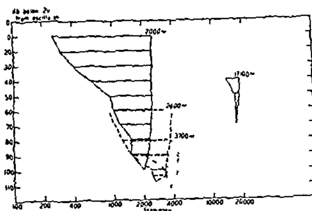


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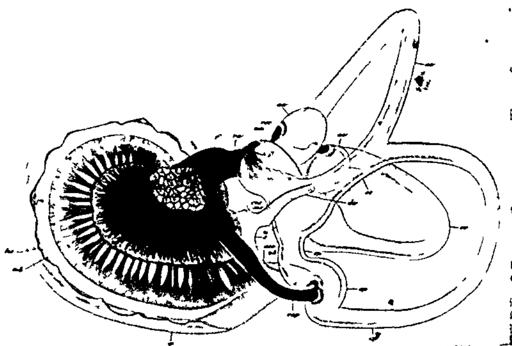


Fig 15 (*G Retzius*)

When the vibrations of the tectorial membrane take a radial course with longitudinal frequency-characteristic phase shifts ("secondary wavelengths") increasing in width from the apex to the base, this is conditioned by the special structure of the modiolus which is built up of radial hard bony lamellae, regularly alternating with soft nerve canals (Fig 15) The vibrations in the labyrinthine fluid, set into motion by the sound, via the middle ear and windows, start a system of regularly radiating vibrations in this structure According to whether these vibrations follow the hard walls or the soft canals, they reach the limbus and tectorial membrane, both of which reflect the same radiating pattern, with a *phase shift owing to the regularly changing conductivity* of the structure and a consequent interfer-

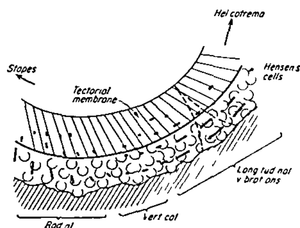


Fig 16

ence The regularity of the system and thereby its form of vibration is accentuated by the situation of the ganglion As demonstrated by Weston, this is in all acoustic epithelia (including also the auditory part of the saccular macula in the ostario physarian fishes) placed close to the inside of the sensory epithelium while the vestibular ganglion is always situated at a greater distance The nerve branches which always increase slightly and regularly in length towards the apex are accurately delimited by the ganglion The interference between these and the intermediate bony *lamellae constitutes, in my opinion*, the frequency discriminating mechanism, no matter how complicated or how simple the structure of the auditory organ in the various vertebrates

Here I have time only to mention that this hearing theory affords a simple explanation of a number of phenomena which have hitherto been unelucidated such as dysacusis diplacusis recruitment and also the sound traumatic deafness lying about one half octave above the *injuring* frequency It is in perfect harmony with v Békésy's experiments (Fig 16)

It may be added that the pressure effect which I have described does not, as originally assumed, entail a deformation of the sensory cell, but a displacement between the cell and the appurtenant Deiters' cell, a mechanism which applies anatomically also to the vestibular organ It would, therefore, be very tempting to accept Professor J A Christiansen's theory (*Acta Oto-laryng*, Suppl *163* 76 (1961)) but only in so far as the giant molecules of hyaluronic acid are placed as bridges crossing the upper part of the space between hair cells and supporting cells the molecules on being bent by the displacement eliciting electrical energy The place thus postulated has just the measure required of 0 5 μ the length of these molecules, as can be seen in the very instructive ultramicroscopical pictures of Flock & Wersäll from the analogous lateral line organ (*Cell Biol* *15*, 19 (1962))

RÉSUMÉ

La structure du labyrinthe montre que la stimulation dépend d'une pression et d'une traction perpendiculaire des membranes cuticulaires Le résultat ne sera pas une déformation mais une dislocation entre une cellule ciliaire et sa cellule supportante dans la partie acoustique comme dans la partie vestibulaire Le mécanisme de la fonction labyrinthaire correspond en beaucoup de respects à celui des autres organes sensoriels qui servent l'orientation et la régulation de position

ZUSAMMENFASSUNG

Der Bau des Labyrinthes zeigt dass seine Reizung auf senkrechtem Druck und Zug der Kutikularmembranen beruht Diese bewirken keine Deformation sondern eine Verschiebung zwischen Haarzelle und zugehöriger Stützzelle im akustischen sowie im vestibulären Teile Der Mechanismus der labyrinthären Funktion stimmt in wesentlichen Beziehungen mit dem der anderen Sinnesorgane für Orientierung und Stellungsregulierung überein

Skovringen 7 Vedbæk Denmark

DISCUSSION

H. Engstrom Dr. Mygind is taking up fundamental problems for discussion problems needing a lot of further documentation. It is necessary to study further the morphological background for dominance in the cochlear and vestibular systems. Dr. Mygind has on many occasions enriched the scientific discussions by interesting ideas and it is a great pleasure to see that this is still the case

H. Davis: Dr. Mygind has mentioned several important principles of the organization and action of the vestibular and auditory systems. Two of these are familiar in classical neurophysiology. One is the organization of the receptor system, with the "dominance" of certain receptor areas, as in the retina of the eye. This principle apparently applies to the cochlea also with the graded thresholds of its sensory units. The organization of the muscular effector system with its proprioceptive mechanism to maintain the upright posture is also familiar.

There is a darker area in the details of the biophysics of the cochlea, with its intricate pattern of fine movements that give us frequency analysis and relative excitation of the hair cells. The best description is given by von Békésy, to whom you have referred. I prefer his description of traveling waves on the basilar membrane, which is confirmed by our own electrical observations, rather than the wave patterns that you suggest, and I find your hypothesis of a "seesaw" movement of the tectorial membrane difficult to accept

As for excitation by pressure on the hair cells versus traction or bending or shearing movements acting on the hairs, this is a detail that is not settled The essential point is that there must be deformation or change of shape at the molecular level This molecular change must act to control the release of additional energy by the hair cell, a sort of biological amplifier to provide the necessary energy to carry out the next step in the excitation of the nerve endings.

A difficult question in the physiology of the cochlea is to explain the very sharp "tuning" of the sensory nerve fibers that was shown to us by Dr Kiang This is very difficult in terms of the biophysical mechanisms as we know them We do not yeat have a satisfactory physical or neurophysiological model, but the sharp tuning is a very clear and important experimental observation

THE MECHANISM OF SECRETION AND ABSORPTION OF ENDOLYMPH IN THE VESTIBULAR APPARATUS[1]

G. F. DOHLMAN
Toronto, Canada

A light and electronmicroscopic study of the specialized cells surrounding the haircell areas of the cristae ampullares and an electronmicroscopic study of the planum semilunatum cells earlier shown to be secretory have been carried out. A viscous secretion *produced in the* haircell region probably by the supporting cells is indicated. This secretion seems to create the "subcupular space". The cells on the slopes of the *cristae* are of two kinds: "dark", osmiophilic cells and "light", osmiophobic cells. Experiments have indicated that the dark cells are absorbing cells and that the light cells probably are secretory. The dark cells have been shown to transport Na^+ ions, whereas the Cl^- ions pass in the intercellular spaces.

It has been shown that the KCl of the endolymph can depolarize the nerve branches of the VIII nerve in the living animal producing nystagmus similar to a Menière attack.

In the inner ear the stria vascularis is generally referred to as the area of endolymph secretion and the saccus endolymphaticus as the place for absorption. However, this study will be concerned with none of them but only with the ampullae of the semicircular canals, and mainly in pigeons *as being the traditional animal for experimental vestibular research.*

Considering the fact that the ampulla from a functional and morphological point of view is the centre where everything necessary for its function is concentrated, it is of interest to record that the whole sensory area is surrounded by specialized cells, which are found in the ampulla only and nowhere else in the canal. The rest of the semicircular canal is a mechanical necessity for increasing an inertial fluid movement.

The first part of the surrounding cell areas to be recognized by the anatomists was the *planum semilunatum*, the *half* moon shaped area, as the name implies, located in the lateral wall of the ampulla.

Radioactively labelled sulphur has in earlier experiments (4) been injected systemically in pigeons and traced by autoradiography as sulphur containing compounds secreted by the cells of the plana semilunata.

The cells in this area are high columnar cells, slowly *decreasing in height*

[1] This investigation was supported by research grant No. 04141 01 from the U.S. National Institutes of Health and by the Canadian Medical Research Council, performed at the Banting Institute, Dept. of Otolaryngology, *and partly aided by resources placed at* disposal by the Defence Medical Research Laboratories, Toronto, Canada.

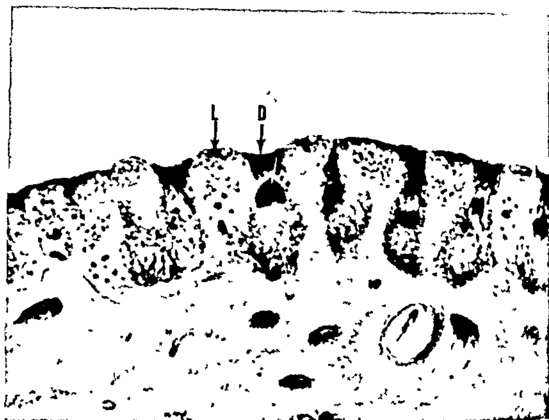


Fig. 1. Epithelium from the slope of the crista. Osmium-fixed, epon embedded. Phase contrast. Regular sequence of "dark" (*D*) cells alternating with "light" cells (*L*).

towards the vertex of the ampulla. In electronmicrograms the supranuclear part of these cells (Fig. 2 A) shows few mitochondria, numerous α-cytomembranes, many vesicles of different size, some arranged in rows, a Golgi apparatus, granules and multivesicular bodies. The infranuclear part (Fig. 2 B) again shows only few mitochondria, few vesicles, several granules and multivesicular bodies. The hyaloplasm is increasingly transparent closer to the slightly folded basement membrane, but no infoldings of the cell membrane as claimed by Bairati & Iurato (2).

On both sides of the crista a totally different kind of cell is seen. These cells have been described by v. Fieandt & Saxen (9) and others as secreting cells and have misleadingly also been called planum semilunatum cells. The difference is not so apparent in lightmicroscopy sections conventionally fixed and stained. However, in osmium-fixed material (Fig. 1) it is evident that this cell layer consists of "dark", highly osmiophilic, cells and "light" cells less osmiophilic and therefore more transparent. They alternate with one another in a regular sequence. This is even more apparent in a cross section of the cells (Fig. 3) where the arrangement and morphological structure of these cells manifest themselves more clearly. The dark cells spread out cytoplasmic lamellae like spokes in a wheel to the surrounding light cells. This very conspicuous pattern of arrangement of the cells where every dark cell is surrounded by light cells and every light cell borders



Fi 2 A Supranuclear part of two planum semilunatum cells Osmium epon Cyto membranes (C) and vesicles (V) indicating secretional activity Golgi apparatus, (G) mitochondria, terminal bar between the cells B) Infranuclear part of planum semilunatum cell Basilar membrane (BM) cell membrane (CM) and intercellular spaces (IC) Mitochondria vesicles



FIG. 3 "Dark" cell in cross section at nuclear level, surrounded by 'light' cells Glutaraldehyde-osmium fixation Embedded in epon

upon dark cells, seems to suggest that these two kinds of cells have different functions but cooperate towards some common object and purpose

Examined in the electronmicroscope, the dark cells can be seen to have a broad border of microvilli protruding into the endolymph (Fig 4), whereas the light cells have a smooth surface The cytoplasm of the dark cell is osmiophilic to such an extent that it is difficult to distinguish any details in the supranuclear part of the cell It is only possible to see that the cytoplasm is tightly packed with mitochondria The light cells contain many vesicles of different size, a few mitochondria and a Golgi apparatus, a few α- and β-cytomembranes, and many granules of different size The infranuclear zone shows even greater structural differences in the two cells (5) The dark cells have an elaborate labyrinth of cytoplasmic lamellae from the nuclear level down to the basement membrane Close to the basement membrane these lamellae can be seen as parallel septa standing on the basement membrane At higher magnification it is evident that these lamellae are filled with mitochondria, enclosed by a system of communicating extra cellular spaces The light cells have no indentations of the cell membrane, they have few mitochondria and numerous small vesicles and many granules often accumulated in great number enclosed by a unit membrane

The very great amount of mitochondria in the dark cells and their



Fig. 4. Surface of "dark" cell. The dark cytoplasm shows an abundance of mitochondria. The surface is covered with microvilli. Glutaraldehyde osmium, Epon.

elaborate system of cytoplasmic lamellae shows great similarity to the cells in the stria vascularis (21), to some cells in the *renal tubuli* (23), *cells in* the choroid plexus (23) and in the ciliary body of the eye (13). They also show a close similarity to the cells in the salt secreting glands *of* the marine birds (6, 7, 14, 15, 31), having to cope with the intake of sea water. These cells are apparently engaged in an energy consuming process with the *special* purpose of moving solutes and solvents through the cell against osmotic and electric gradients. This appearance of the dark cells in the labyrinth and the presence of a pronounced border of microvilli at the surface is very suggestive of a resorptive function.

The unique composition of the endolymph with its high potassium and low sodium concentration could provide *a reason for* an absorptive function operating in the removal of sodium ions from the endolymph (5).

Experiments were therefore *made* with *injections* of sodium chloride solutions of different concentrations *(0.5%–5%)* into the endolymph. This produced a pronounced increase of vacuoles in the dark *cells*.

If methylene blue was added to the injected sodium chloride solution blue inclusions in the dark *cells could* be demonstrated by light microscopy. About 30 min. after the injection of methylene *blue* the dye could be found also in the connective tissue and in the walls of the capillaries underneath these cells. In electronmicrograms the methylene blue crystals could be



FIG. 3. "Dark" cell in cross section at nuclear level, surrounded by "light" cells. Glutaraldehyde osmium fixation. Embedded in epon.

upon dark cells, seems to suggest that these two kinds of cells have different functions but cooperate towards some common object and purpose.

Examined in the electronmicroscope, the dark cells can be seen to have a broad border of microvilli protruding into the endolymph (Fig. 4), whereas the light cells have a smooth surface. The cytoplasm of the dark cell is osmiophilic to such an extent that it is difficult to distinguish any details in the supranuclear part of the cell. It is only possible to see that the cytoplasm is tightly packed with mitochondria. The light cells contain many vesicles of different size, a few mitochondria and a Golgi apparatus, a few α- and β cytomembranes, and many granules of different size. The infranuclear zone shows even greater structural differences in the two cells (5). The dark cells have an elaborate labyrinth of cytoplasmic lamellae from the nuclear level down to the basement membrane. Close to the basement membrane these lamellae can be seen as parallel septa standing on the basement membrane. At higher magnification it is evident that these lamellae are filled with mitochondria, enclosed by a system of communicating extra cellular spaces. The light cells have no indentations of the cell membrane, they have few mitochondria and numerous small vesicles and many granules often accumulated in great number enclosed by a unit membrane.

The very great amount of mitochondria in the dark cells and their



Fig. 4. Surface of "dark" cell. The dark cytoplasm shows an abundance of mitochondria. *The surface is covered with microvilli.* Glutaraldehyde osmium. Epon.

elaborate system of cytoplasmic lamellae shows great similarity to the cells in the stria vascularis (29), to some cells in the renal tubuli (23), *cells in the choroid plexus* (23) and in the ciliary body of the eye (13). *They also* show a close similarity to the cells in the salt secreting *glands of the marine* birds (6, 7, 14, 15, 35), *having to* cope with the intake of sea water. *These* cells are apparently engaged in an energy consuming process with *the special* purpose of moving solutes and solvents through the cell against *osmotic* and electric gradients. This appearance of the dark cells in the labyrinth and the presence of a pronounced border of microvilli at the surface is very suggestive of a resorptive function.

The unique composition of the endolymph with *its high* potassium and low sodium concentration *could provide* a reason for an absorptive function operating in the *removal* of sodium ions from the endolymph (5).

Experiments were therefore *made* with injections of sodium chloride solutions of different concentrations (0.5%–5%) *into the* endolymph. This produced a pronounced increase of vacuoles in the *dark cells*.

If methylene blue was *added* to the injected sodium chloride solution, blue inclusions in the dark cells could be *demonstrated* by light microscopy. About 30 min. after the injection of methylene *blue*, the dye could be found also in the connective tissue and in the walls of the capillaries underneath these cells. In electronmicrograms the *methylene* blue crystals could be



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Fig. 6. The chlorine is precipitated with silverlactate. The silver chloride grains are nearly exclusively found in the intercellular spaces (between the cytoplasmic lamellae) and in the vacuoles of the "dark" cells.

With this method the sodium ions were found to be precipitated intracellularly in the dark cells in the cytoplasm and in the mitochondria (Fig. 5). Precipitating the chlorine ions with silverlactate in the same way, these ions could be traced mostly to the intercellular spaces and to some extent also to the *vacuoles in the dark cells* (Fig. 6).

In both experiments the precipitations were exclusively related to the dark cells; only occasionally could there be found some single grains in the light cells.

If sodium chloride was injected into the endolymph before these precipitation experiments, this did not increase the precipitations in the section to any appreciable amount in comparison with the non-injected controls. This could be due to deficiencies in the method to give quantitative results. An alternative explanation would imply that these cells already work at the level of their possible efficiency and that the intensity of their absorptive function can be changed only within narrow limits.

However, *the considerably increased number of* vacuoles which could be recorded after sodium chloride injections seems to indicate that the fluid transport through the cells had been enhanced. This might infer that the speed of transfer of solvent and solutes could have been increased and therefore also the amount passed through the cell per unit time without increas



Fi[illegible] Dark (*DC*) and light (*LC*) cells. S[illegible] is precipitated with [illegible]. The precipitations are nearly exclusively located in the dark cells.

traced to the vacuoles in the dark cells. Methylene blue could not be found in any of the light cells.

An attempt was then made to inject a solution of radioactively labelled sodium Na[illegible] as sodium chloride. Due to the solubility of the salt special precautions to fix and dehydrate at low temperature made it possible to preserve some of the radioactive ions to yield autoradiographs ([illegible]) which also showed the same localization only to the dark cells. Further in an attempt at precipitating the sodium and the chlorine ions in the tissue a method described by Komnick (14) was used.

During fixation with buffered osmium tetroxide the sodium ions were precipitated by adding potassium antimony hexahydroxide to the solution. This impaired the possibilities for a proper fixation considerably but the main outlines of the cell constituents could still be preserved.

in pigeons does not seem to have been described in other investigations on similar cell groups. The anatomical pattern of this epithelium might be more pronounced in birds but the principle of absorbing and secreting functions of the cells surrounding the sensory areas might in all probability prove to be the same also in other species. In the human labyrinth a similar arrangement of "dark" and "light" cells has been shown to me by Dr J. Larkowski from his investigations on operated cases of Ménière's disease.

It is obvious that much more investigation into the mechanism of the secretory and absorbing functions is necessary to understand the balance of these two functions under normal conditions and the imbalance in diseases such as Ménière's. However, so far the finding of absorbing cells in the labyrinth might explain why blocking of the endolymphatic duct failed to produce an immediate distention of the membraneous labyrinth (18). Therefore it seems to be even more important to investigate the factors regulating these processes.

However, other experiments are also necessary. Even if this is outside the scope of the title of this paper, I would like to shortly mention one experiment which might have some relevance to the circulation of endolymph.

During experiments on frogs recording the frequency of action potentials in the ampullary nerve together with Dr Cesar Fernandez in Chicago we found repeatedly that the action potentials decreased or disappeared if the endolymph or a KCl solution of a concentration like that of the endolymph (1.1%) leaked out round the nerve. In the living animal this would have an effect like that of a labyrinthectomy or anesthetizing the labyrinth with cocain etc.

Experiments were therefore made in living animals using a 1.1% KCl solution applied to the perilymphatic space. First, labyrinthine fistulas were made in the canals on pigeons and KCl was applied to the fistula. This gave no effect. Apparently the membraneous ampulla provides a mechanical block for the diffusion of the KCl. However, if the columella was removed allowing the solution to diffuse into the vestibule a long lasting nystagmus was produced.

Together with Dr Walter Johnson these experiments were continued on squirrel monkeys. Only if the vestibule was opened through the oval window it was possible to produce a nystagmus. The nerves to the ampullae and utricle pass through the perilymphatic space on the vestibular side of the ampullae and can apparently be reached by the solution only from this side. After a time of latency of 1' to several min a nystagmus started and increased in intensity during the next few minutes and continued for an hour or more in our experiment. If the KCl solution was then removed and the middle ear cavity flushed with normal saline solution the nystagmus diminished slowly and had totally disappeared after 20–25 min.

The distention of the endolymphatic spaces in Ménière's disease is a fact (11, 12, 17, 20, 21), and rupture of the distended weak spots in the walls of the endolymphatic sacs seems to be a probable sequence of an incidental

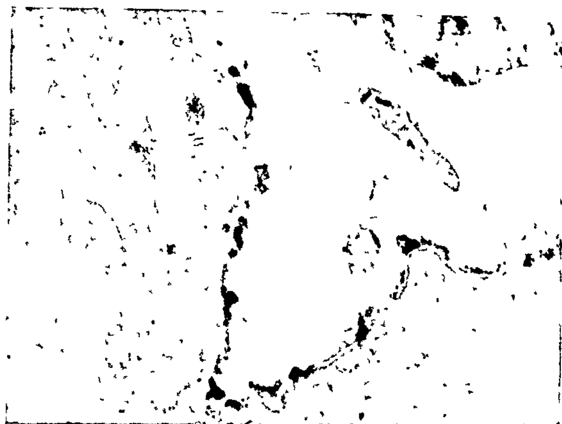


FIG. 7. Silver chloride precipitations in the intercellular spaces between the "dark" and the "light" cells.

ing the concentration of sodium chloride actually present in the cell at any moment. The only change in the light cells which could be recorded was an increase in the number and size of vesicles.

Therefore, the results of these experiments seem to indicate that the "dark" cells are engaged in the absorption and removal of sodium and chlorine ions, in the transfer of water and also in the removal of foreign watersoluble substances, as for instance methylene blue. The second category of cells, the "light" cells, surround the "dark" cells and are intimately connected with these cells by means of an abundance of villi-like processes interdigitating with one another. This whole arrangement gives an impression of co-operation between these two types of cells. It is therefore assumed that certain ions and fluids absorbed by the dark cells may be passed to the light cells to be secreted back into the endolymph. Further, the great amount of granules and multivesicular bodies in these cells could indicate that they also contribute by producing other substances for their secretion.

Dark and light cells have earlier been described in areas which have been regarded to be engaged in the transport of solvents and solutes among others in the labyrinth and stria vascularis by C. A. Smith (27, 28, 29). However, the strikingly regular pattern in the arrangement of these cells

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increase in endolymphatic pressure. Lindsay and Schuknecht have produced strong evidence in favour of this assumption.

A sudden rupture of the endolymphatic spaces could be assumed to produce a Ménière attack in several ways. Schuknecht has assumed a collapse of the membraneous ampulla with a bending of the cupula as a probable sequence of a rupture of the membraneous wall. However, the membraneous ampulla is tied to the bony wall by a dense network of perilymphatic connective tissue. Further, the reaction due to a sudden bending of the cupula is a matter of milliseconds and will rapidly decrease due to adaptation.

In cases of Ménière's syndrome the attacks very rarely start apoplectiform, usually the patients have time to sit or lie down before the vertigo has reached an incapacitating intensity and the nystagmus and vertigo usually last longer than it takes for the cupular reaction to subside.

The possibility of a temporary depolarization of the nerves by the KCl of the endolymph, which Schuknecht also mentions, therefore seems to offer a more likely explanation for the mechanism of a Ménière attack even if the mechanical cupula stimulation could be an alternative explanation for "otolithic catastrophes" and short vertiginous episodes.

Evidence brought forward by Lindsay suggests that the distention of the endolymphatic system starts in the cochlea because Reissner's membrane appears to be the least resistant part of the wall. The distended Reissner's membrane then usually fills and blocks the scala vestibuli. A rupture of this membrane in the apical turn would imply that the outflowing endolymph enters the scala tympani through the helicotrema. The scala tympani ends blindly at the round window with no connections with the perilymphatic space of the vestibule and has only one possible outlet through the perilymphatic duct and the arachnoid space. This will probably provide a slow elimination of the endolymph leaking through the ruptured Reissner's membrane.

It has been shown by Tasaki & Fernandez and Tasaki, Davis & Eldridge (33, 34) that even a 1:3 dilution of the KCl concentration of the endolymph penetrates the basilar membrane from the scala tympani and suppresses the neural and microphonic responses temporarily in the elements reached by the KCl solution. A rupture at the helicotrema would therefore result in a suppression of neural transmission mainly in the upper coils of the cochlea.

This would explain the characteristic, fluctuating low-tone hearing loss for air-conduction as well as bone-conduction starting in early stages of Ménière's disease before involvement of the vestibular organ. If the process continues distending also the utricle and saccule with herniations and ruptures as a consequence, the distended endolymphatic vestibular spaces will have reduced the perilymphatic cavity of the vestibule to thin lamellar dimensions. A rupture might then imply that the endolymph enters the perilymphatic spaces without being diluted to any appreciable amount. The nerves passing from their bony canals through the perilymphatic tissue to

the ampullae and the vestibular sacs must therefore be exposed to the depolarizing influence of the KCl of the outflowing endolymph, facilitating or inactivating the nerve activity

In conclusion, our experiments on pigeons and monkeys might *therefore* suggest that a similar mechanism might be operating in those cases of Ménière's disease where a rupture of Reissner's membrane at the helicotrema produces a low tone hearing loss and ruptures in the walls of the vestibular sacs may produce a temporary increase or decrease *in the neural frequency of action potentials in one* or several of the vestibular nerve branches resulting in symptoms of a Ménière attack

Neuro vegetative instability angiospasm, allergic or metabolic disturbances have been mentioned as etiological factors and supported by clinical *observations All these factors could* probably be of importance for the creation of an imbalance of secretory and absorbing processes which are the basis for accumulation of endolymph and the distentions of the membraneous labyrinth A reasonable explanation for the low tone hearing loss and *for the elicitation of the attacks of vertigo* cannot be provided by these disturbances alone An alternative has therefore been presented to explain at least one type of the symptoms in Ménière's disease

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I am deeply grateful for all help from Prof P Ireland which has made it possible to fulfil this investigation to Dr Walter Johnson *for close cooperation* and to Dr J Larkastudy for fruitful discussions For skilled technical help I am indebted to the R Narvarande and Mr A Brown

RESUME

L'étude en microscopie optique et électronique des zones cellulaires specialisees entourant les cretes ampullaires des canaux semi circulaires a montre que ces zones sont constituees de cellules secretrices et absorbantes

Les ions absorbes sont visibles dans les cellules

ZUSAMMENFASSUNG

Mikroskopische und elektronenmikroskopische Untersuchungen *der Zellregionen* welche die Crista ampullaris umgeben haben gezeigt dass sie sowohl aus *sekretorischen wie aus absorbierenden Zellen* bestehen Die absorbierten Ionen wurden in den Zellen nachgewiesen

REFERENCES

1 ALTMANN, F., and WALTNER, J. G., 1950 Further investigations on the physiology of the *labyrinthine fluids Ann Otol Rhin Laryng*, 59 657
2. BARNES, A., and SJ...TO, S., 1960 The ultrastructural organization of *Hana semilunata Exp Cell Res* 20 77

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30 SCHUKNECHT, H. F., BENITEZ, J. T., and BECKHUIS, J., 1962. Further observations on the pathology of Menière's disease. *Ann. Otol.* 71, 1039.
31 SCHUKNECHT, H. F., and KIMURA, R. S., Functional and histologic findings after obliteration of the periotic duct and endolymphatic sac in sound condition cats. *Laryngoscope* 63, 1170.
32 SCHUKNECHT, H. F., and SEAA EL SEIFI, 1963. Experimental observations on the fluid physiology of the inner ear. *Ann. Otol.* 72, 687.
33 TASAKI, I., and FERNANDEZ, C., 1952. *J. Neurophysiol.* 15, 497.
34 TASAKI, I., DAVIS, H., and ELDREDGE, D. H., 1954. Exploration of cochlear potentials in guinea pigs with a microelectrode. *J. Acoust. Soc. Amer.* 26, 765.
35 TEMPLETON, J. R., 1964. Nasal salt excretion in terrestial lizards. *Comp. Biochem. Physiol.* 11, 223-230.
36 TONNDORF, J., 1957. The mechanism of hearing loss in early cases of endolymphatic hydrops. *Ann. Otol.* 66, 766.
37 TUMARKIN, A., 1936. Otolithic catastrophe. A new syndrome. *Brit. Med. J.*, 2, 175.
38 WILLIAMS, H. L., 1952. *Menière's Disease*. Chas. C. Thomas, Springfield, Ill.
39 WILLIAMS, H. L., LINDSAY, J. R., WALSH, TH. L., HOOPLE, G. D., LATHROP, F. D., and HILL, F. T., 1956. Symposium: Menière's Disease. *Trans. Amer. Acad. Ophtal. Otolaryng.* 60, 167.
40 YAMAMOTO, K., YOSHIMAN, N., 1964. Electronmicroscopic studies on the functions of the stria vascularis and the spiral ligament in the inner ear. *Ann. Otol.*, 73, 332.

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DISCUSSION

H. Davis: Prof. Dohlman has made important advances by applying methods of histochemistry and electron microscopy. He demonstrates specialization of function of different types of cell and even within different parts of cells. Special chemical (metabolic) activity is necessary to maintain the very special anatomical structure and chemical composition of our delicate sense organs. It is very reasonable to expect occasional disorders of these special functions, and I like the hypothesis that Menière's syndrome may represent such a chemical secretory disorder.

Nature is kind to us in the anatomical arrangement of the specialized secretory cells in the vestibule and cochlea where they are neatly arranged for microscopic studies and biochemical experiments. Unfortunately, however, it is difficult enough to collect perilymph for chemical analysis and it is almost impossible to collect endolymph in sufficient quantities and without contamination.

J. Lundquist: On the basis of India ink experiments on guinea pigs some ten years ago I put forward the theory that absorptive and secretory forces in the endolymphatic duct were not refined to the endolymphatic sac and the stria alone but took place elsewhere in the duct. Two days ago Professor Borghesan suggested a secretion to take place in the external spiral sulcus and to-day Professor Dohlman has found evidence of a similar phenomenon in the cell areas surrounding the crista of the ampullae in the semicircular canals.

Now Professor Dohlman emphasizes that both absorptive and secretory processes take place side by side, and I think this is very important in our understanding of the fluid exchange in the labyrinth.

Even if I am aware of the impossibility of drawing any conclusion of what is

3 BAIRATI A, 1960 Recentes connaissances sur la structure submicroscopique les organes du vestibule *Acta Otolaryng (Stockh)* Suppl *163* 9
4 DOHLMAN, G F, ORMEROD, F G, and MCCLAY K 1959 The secretory epithelium of the internal ear *Acta Oto laryng (Stockh)*, *50* 243
5 DOHLMAN G F Secretion and Absorption of Endolymph *Ann Otol 73* 708 1964
6 DOYLE W L 1960 The principal cells of the salt gland of marine birds *Exp Cell Res 21* 386 393
6 *a* — 1962 Tubule cells of the rectal salt gland of Urolophus *Amer J Anat 111* 223–238
7 ELLIS RICHARD A and ABEL, JOHN H 1964 Intercellular channels in the salt secreting glands of marine turtles *Science, 144* 1340–1342
8 V EILANDT, H and SAXEN, A 1936–37 Beitrage zur Histologie der Stria vascularis und der Prominentia spiralis bei Saugern *Z Anat Entw Gesch 106* 425
9 — 1948 Histological studies of endolymph secretion and resorption in the inner ear *Acta Otolaryng (Stockh)*, Suppl *70*
10 GUILD S 1927 Circulation of the endolymph *Amer J Anat 39* 57
11 HALLPIKE C S, and CAIRNS H 1938 Observations of the pathology of Menieres disease *J Laryng 53* 625
12 HALLPIKE C S and WRIGHT, A J 1940 Histological changes of cases of Menieres
13 HOLMBERG A 1959 Ultrastructure of the ciliary epithelium *Arch Ophthal 62* 935
14 KOMNICK H 1962 Elektronenmikroskopische Lokalisation von Na⁺ und Cl⁻ in Zellen und Geweben *Protoplasma 55* 414
14 *a* — 1963 Zur funktionellen Morphologie der Salzsaure Produktion in der Magenschleimhaut *Histochemie 3* 354
15 KOMNICK H and KOMNICK U 1963 Elektronenmikroskopische Untersuchungen z funktionellen Morphologie des Ionentransportes in der Salzdrüse v Larus Argent *Z Zellforsch 60* 163
16 LAWRENCE M and MCCABE B 1959 Inner ear mechanics and deafness *J A M A 171* 1927
17 LINDSAY J R 1942 Labyrinthine dropsy and Menieres disease *Arch Oto laryng (Chic) 35* 853
18 — 1947 Effect of obliteration of the endolymphatic sac and duct in the monkey *Arch Otolaryng (Chic) 45* 1
19 — 1960 Menieres disease histopathological observations *Arch Otolaryng (Chic) 71* 500
20 — 1960 Hydrops of the labyrinth *Arch Otolaryng (Chic) 71* 500
21 LINDSAY J R and v SCHULTHESS G 1958 An unusual case of labyrinthine hydrops *Acta Otolaryng (Stockh) 49* 315
22 MCNALLY W J 1926 Experiments on the saccus endolymphaticus in the rabbit *J Laryng 41* 343
23 PEASE D C, 1955 Electron microscopy of the tubular cells of the kidney cortex *Anat Rec 121* 723
24 RETZIUS G Gehörorgan der Wirbelthiere Vogel und Reptilien II Stockholm 1884
25 ROLLIN H 1940 Zur Kenntnis des Labyrinth Hydrops des durch ihn bedingten Meniere *Hals Nas u Ohrenar 31* 73
26 SAXEN A 1951 Histological study of endolymph secretion and resorption in the inner ear *Acta Otolaryng (Stockh) 31* 23
27 SMITH C A 1955 Electron microscopic studies of the organ of Corti *Anat Rec 121* 451
28 — 1956 Microscopic structure of the utricle *Ann Otol 65* 450
29 — 1957 Structure of the stria vascularis and the spiral prominence *Ann Otol Rhinol Laryng 66* 521

30 Schuknecht H F, Benitez J T, and Beekhuis J, 1962 Further observations on the pathology of Meniere's disease *Ann Otol* 71 1039
31 Schuknecht H F and Kimura R S, *Functional and histologic findings after obliteration of the periotic duct and endolymphatic sac in sound conditioned cats* *Laryngoscope* 63 1170
32 Schuknecht H F and Alan El Seifi, 1963 Experimental observations on the fluid physiology of the inner ear *Ann Otol* 72 687
33 Tasaki I, and Fernandez, C, 1952 *J Neurophysiol*, 15 497
34 Tasaki I, Davis, H, and Eldredge, D H, 1954 Exploration of cochlear potentials in guinea pigs with a microelectrode *J Acoust Soc Amer*, 26 765
35 Templeton J R, 1964 Nasal salt excretion in terrestial lizards Comp *Biochem Physiol*, 11 223 230
36 Tonndorf J, 1957 The mechanism of hearing loss in early cases of endolymphatic hydrops *Ann Otol* 66 766
37 Tumarkin A, 1936 *Otolithic catastrophe* A new syndrome *Brit Med J* 2 175
38 Williams H L, 1952 *Meniere's Disease* Chas C Thomas Springfield Ill
39 Williams, H L, Lindsay J R, Walsh Th E, Hoople G D, Lathrop F D, and [illegible] J T, 1956 Symposium Ménière's Disease *Trans Amer Acad Ophthal Otolaryng* 60 167
40 Yamamoto K, Yoshiaki, N 1964 Electronmicroscopic studies on the functions of the stria vascularis and the spiral ligament in the inner ear *Ann Otol* 73 332

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3 Bairati A 1960 Récentes connaissances sur la structure submicroscopique des organes du vestibule *Acta Otolaryng (Stockh)*, Suppl *163*, 9
4 Dohlman, G F, Ormerod, F G, and McClay, K, 1959 The secretory epithelium of the internal ear *Acta Oto laryng (Stockh)*, *50*, 243
5 Dohlman G F Secretion and Absorption of Endolymph *Ann Otol* 73 708, 1964
6 Doyle, W L 1960 The principal cells of the salt gland of marine birds *Exp Cell Res*, *21* 386–393
6a — 1962 Tubule cells of the rectal salt gland of Urolophus *Amer J Anat* *111* 223–238
7 Ellis, Richard A and Abel, John H, 1964 Intercellular channels in the salt secreting glands of marine turtles *Science*, *144*, 1340–1342
8 v Eifandt, H, and Saxen, A, 1936–37 Beiträge zur Histologie der Stria vascularis und der Prominentia spiralis bei Säugern *Z J Anat Entw Gesch*, *106* 425
9 — 1948 Histological studies of endolymph secretion and resorption in the inner ear *Acta Otolaryng (Stockh)*, Suppl *70*
10 Guild, S, 1927 Circulation of the endolymph *Amer J Anat* 39 57
11 Hallpike C S, and Cairns H 1938 Observations of the pathology of Menieres disease *J Laryng* 53, 625
12 Hallpike C S, and Wright, A J 1940 Histological changes of cases of Menieres
13 Holmberg A, 1959 Ultrastructure of the ciliary epithelium *Arch Ophthal* 62 935
14 Komnick H, 1962 Elektronenmikroskopische Lokalisation von Na⁺ und Cl⁻ in Zellen und Geweben *Protoplasma* 55, 414
14a — 1963 Zur funktionellen Morphologie der Salzsäure Produktion in der Magenschleimhaut *Histochemie*, *3* 354
15 Komnick, H, and Komnick U, 1963 Elektronenmikroskopische Untersuchungen z funktionellen Morphologie des Ionentransportes in der Salzdrüse v Larus Argent *Z Zellforsch* 60 163
16 Lawrence M, and McCabe B, 1959 Inner ear mechanics and deafness *J A M A*, *171* 1927
17 Lindsay, J R 1942 Labyrinthine dropsy and Menière's disease *Arch Oto laryng (Chic)* 35 853
18 — 1947 Effect of obliteration of the endolymphatic sac and duct in the monkey *Arch Otolaryng (Chic)* 45 1
19 — 1960 Menière's disease histopathological observations *Arch Otolaryng (Chic)* *71* 500
20 — 1960 Hydrops of the labyrinth *Arch Otolaryng (Chic)* *71* 500
21 Lindsay J R and v Schulthess G 1958 An unusual case of labyrinthine hydrops *Acta Otolaryng (Stockh)* 49 315
22 McNally W J 1926 Experiments on the saccus endolymphaticus in the rabbit *J Laryng* 41 349
23 Pease D C, 1955 Electron microscopy of the tubular cells of the kidney cortex *Anat Rec* *121* 723
24 Retzius G Gehörorgan der Wirbelthiere Vögel und Reptilien II Stockholm 1884
25 Rollin H, 1940 Zur Kenntnis des Labyrinth hydrops des durch ihn bedingten Menière *Hals Nas u Ohrenar I* 31 73
26 Saxen A, 1951 Histological study of endolymph secretion and resorption in the inner ear *Acta Otolaryng (Stockh)* 41 23
27 Smith C A, 1955 Electron microscopic studies of the organ of Corti *Anat Rec* 121 451
28 — 1956 Microscopic structure of the utricle *Ann Otol* 65 450
29 — 1957 Structure of the stria vascularis and the spiral prominence *Ann Otol Rhinol Laryng* 66 521

UNTERSUCHUNG DER PERILYMPHE NACH STAPEDEKTOMIE IN OTOSKLEROSEFÄLLEN[1]

L. Rüedi, M. C. Sanz und U. Fisch
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Aus der Otorhinolaryngologischen Klinik der Universität Zürich
(Dir. Prof. Dr. L. Rüedi)

In 155 Otosklerosefällen wird im Verlauf der Stapedektomie Perilymphe entnommen und in 302 Untersuchungen wird der Gehalt an K^+, Na^+, Cl^-, Ca^{++}, alkalischer Phosphatase, Glukose und Proteine bestimmt.

Dabei bestätigt sich das Auftreten von alkalischer Phosphatase in der Otosklerose-Perilymphe. Die Ca-Werte sind erniedrigt und weisen eine unregelmässige Verteilung auf. Erstmals wird eine signifikante Vermehrung des durchschnittlichen K-Gehaltes und Proteingehaltes festgestellt. Die Entstehung der K-Vermehrung wird diskutiert. Statistisch ist eine *Korrelation nachweisbar* zwischen dem erhöhten K^+-Gehalt und dem erhöhten Gehalt an Proteinen einerseits und dem praeoperativen Hörverlust für die Knochenleitung bei 4000 Hz andererseits. Demgegenüber gelingt es *nicht, eine entsprechende Korrelation zu zeigen* zwischen der K- und Proteinvermehrung und den prae- und postoperativen Störungen des Vestibularapparates.

Dank den Arbeiten von Smith und Mitarb. (1954), den Beiträgen von Citron und Mitarb. (1956), und den Untersuchungen von Rauch (1964) wissen wir, dass in der Perilymphe und im Liquor cerebrospinalis des Meerschweinchens, der Katze und des Menschen praktisch dieselbe Konzentration von Na, K und Cl vorhanden ist, entsprechend dem Elektrolytgehalt extracellulärer Flüssigkeiten. Demgegenüber findet sich in der Endolymphe ca. 30mal mehr K und 10mal weniger Na als in der Perilymphe. Normalerweise ist in der Perilymphe und im Liquor keine alkalische Phosphatase nachweisbar.

Nachdem im Verlauf einer Stapedektomie regelmässig der Perilymphraum eröffnet wird, liegt es nahe, Perilymphuntersuchungen in Otosklerosefällen vorzunehmen. In Zusammenarbeit mit S. Rauch haben wir im April 1960 in zwei blutfreien Perilymphproben von Otosklerosefällen alkalische Phosphatase (1.4 Bodansky-Einheiten und 10.1 Bodansky-Einheiten) gefunden. S. Rauch hat diese Untersuchungen mit Wullstein, Kley und Koestlin (1960)

[1] Die Durchführung dieser Arbeit wurde dank der Unterstützung durch den Schweizerischen Nationalfonds ermöglicht.

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M. Arslan. To the very interesting results exposed by Dohlman on the subject of the endolymph secretion I should like to add that, at the ENT Dpt. of Padua University, we have been working for three years on the following experimental procedure, directed to provoke an artificial change of the osmotic pressure of the perilymph and of the endolymph putting a NaCl crystal on the round window membrane of a cat, one can observe the perilymph coming out as a consequence of a semipermeable function of this membrane (the hypotonic perilymph is directed to the hypertonic fluid existing on the round window membrane) By this experiment, histological observations made in the different phases reveal a collapse of the endolymphatic duct, and later an hydrops of the same canal These two opposite pathologic pictures correspond to an opposite behaviour of the cochlear microphonics, of the potential currents of a deitersian units, and finally, in the living animal to a typical Meniere's attack, which in the first phase is characterized by an "irritative" vestibular syndrome, and in the second phase by a "paralytic" syndrome All these phenomena depend on the osmotic sudden variations in the balance between perilymph and endolymph

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Zu Dr *Arnvig* möchte ich nur kurz bemerken, dass die Frage von Sekretion und Absorption ausserdem auch den Saccus endolymphaticus mit berücksichtigen muss, besonders wenn korpuskuläre Elemente wie die Kohlepartikeln in der Tusche zugeführt werden Diese werden meiner Meinung nach im Saccus resorbiert

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Mikrochemische Untersuchungsmethoden

Die verwendeten Geräte und Apparate sind Pipetten nach Sanz (1957 und 1959), Flammenphotometer Beckman B, Spektrocolorimeter Beckman — Spinco Mod 151, Mikrotitrator Beckman — Spinco Mod 153, Ultraviolettlampe Pleuger, Brussel (fur die Titration von Calcium), Mikrozentrifuge Beckman — Spinco, Mikrothermostat Rotax, Basel, Mikromixer Beckman — Spinco Mod 154

Zur möglichst genauen Bestimmung der Zusammensetzung der Perilymphe mussten 2 wichtige Fehlerquellen eliminiert werden, nämlich die Beimischung von Spulflussigkeit wahrend der Operation und eine solche von Blut Die Zugabe von Lithium, welches im biologischen Milieu nicht vorkommt, zur Spulflussigkeit erlaubte deren quantitative Erfassung Mit einer verfeinerten Benzidinmethode gelang es uns, auch Blutbeimischungen bis herunter auf 0,1% zu bestimmen Alle angegebenen Resultate sind nach Anbringen der zwei Korrekturen berechnet worden

Die Bestimmung der Alkalimetalle erfolgte durch Flammenphotometrie

Natrium 1 38 μl Perilymphe, 300 μl H_2O bidest Messung bei 589 nm

Kalium 1 38 μl Perilymphe, 200 μl H_2O bidest Messung bei 766 nm

Kontrolle Lithium 1 38 μl Perilymphe, 500 μl H_2O bidest Messung bei 670 nm

Kontrolle *Blut* Benzidintest (Crosby und Furth 1956), modifiziert nach Sanz, 0,5 μl Perilymphe (oder Standard), 20 μl H_2O bidest, mischen, davon 1,0 μl, 50 μl Benzidin 1% in 90%iger Essigsaure V/V, 50 μl H_2O_2 0 25%

Nach genau 20 Minuten (Stoppuhr) Zugabe von 125 μl Na acetat 1% zum Abstoppen der Reaktion Die Absorption wird bei 515 nm abgelesen

Standard-Vorbereitung

Als Standard dient das Blut des betreffenden Patienten, das verdunnt wird in einer Reihe von 2 10% Blutgehalt (je nach Bedarf bis 20%)

Calcium Titration unter der Fluoreszenzlampe mit EDTA und Calcein als Indikator Das Milieu muss stark alkalisch sein

Chlorid Titration mit Quecksilbernitrat und s diphenylcarbazon als Indikator nach Ansauern mit Salpetersaure

Glucose Ortho toluidinmethode nach Hultman (1959), Hyvarinen und Nikkila (1962) modifiziert nach Sanz 2 5 μl Perilymphe, 50 μl Trichloressigsaure 3% *mischen zentrifugieren, 40 μl* uberstehende Losung 120 μl o Toluidinreagenz (siehe Hyvarinen und Nikkila (1962)), mischen, 10 Minuten in kochendem Wasserbad abkuhlen photometrieren bei 630 nm

Alkalische Phosphatase p Nitrophenylphosphat wird als Substrat verwendet, *Inkubation* 30 Minuten bei 37°C

Protein Turbidimetrische Methode 10 μl Perilymphe, 20 μl Rhodoviol 0 1 *g 100 ml, 100 μl* Sulfosalicylsaure 3 6 g/100 ml, mischen, nach 10 Minuten bei 420 nm photometrieren

Untersuchungsresultate

a) Gehalt an Elektrolyten

In der Abb 1 geben die weissen Saulen in der 1 Kolonne den durchschnittlichen Gehalt der normalen menschlichen Perilymphe an Na^+, Cl^-, Ca^{++} und K^+ in mval/l an In den weissen Saulen der zweiten und dritten

TABELLE I. *Otosklerose-Patienten mit Perilymph-Entnahme 155*

	Perilymph-Bestimmungen
K^+	121
Na^+	38
Cl^-	31
Ca^{++}	25
Glucose	27
Alk. Phosphatase	30
Proteine	30
Total	302

fortgesetzt. Wiederum ist in 10 Otosklerosefällen alkalische Phosphatase in der Perilymphe festgestellt worden.

Seither haben wir in 155 Otosklerosefällen Perilymphe entnommen und 302 Untersuchungen zur Bestimmung der K^+-, Na^+-, Cl^-- und Ca^+-Werte und des Gehaltes an alkalischer Phosphatase, Glukose und Proteinen durchgeführt.

Technik der Perilymphgewinnung

Die Stapedektomie wird eingeleitet durch eine erste endaurale Inzision, welche die hintere Hälfte des häutigen Gehörganges auf der Höhe des knöchernen Kanals zirkulär durchtrennt. Danach erfolgt mit Hilfe einer zweiten retroaurikulären Inzision die Darstellung und die Ablösung der Gehörgangshaut bis zum knöchernen Margo. Der knöcherne Gehörgang wird mit dem Bohrer geglättet und etwas erweitert und der knöcherne Margo zur besseren Übersicht des Fensterbereiches mit dem Diamantbohrer abgetragen. Nach der Durchtrennung des m. stapedius und der Abtragung des Processus pyramidalis ist der im ovalen Fenster otosklerotisch fixierte Stapes vollständig überschaubar und beide Crura können bis zur Fussplatte verfolgt werden. Nun wird zuerst das Crus ant. dann das Crus post. möglichst nahe der Fussplatte durchtrennt, worauf der Oberbau des Stapes aus der gelenkigen Verbindung mit dem langen Ambossfortsatz gelöst und herausgehoben wird. Nach Entfernung der Schleimhaut aus dem Bereich der ovalen Fensternische wird die vor der Operation entnommene Vene geglättet und zugeschnitten. Inzwischen wird eine vollständige Blutstillung und Trockenlegung der Fensternische mit Gelfoam-Einlagen angestrebt. Erst nachdem die Fensternische blutleer ist, durchbohrt man die Stapesfussplatte mit einer Nadel, worauf ein grösseres Plattenstück entfernt wird. Zur Gewinnung der austretenden Perilymphe eignet sich am besten ein kapillares Röhrchen aus Kalium-freiem Pyrexglas, welches in einen Polyäthylenschlauch mündet. Der Operateur nimmt diesen Polyäthylenschlauch in den Mund und saugt unter Sicht (Mikroskop) die Perilymphe in die Glaskapillare, wobei diese Kapillare nur bis zum Rand des ovalen Fensters vorgeschoben werden darf. Entnahmemenge: mindestens 1 λ. Während der Operation wird eine 0,5%ige Lithium-Chlorid-Spülflüssigkeit verwendet.

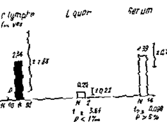
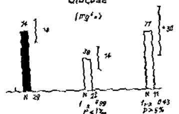
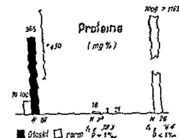
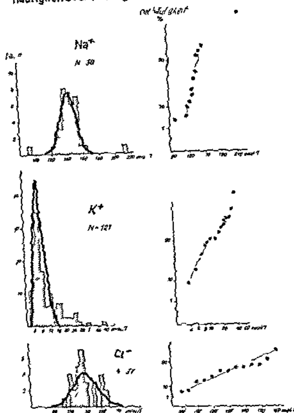





Abb 2 Abb 3

Abb 2 Der durchschnittliche Gehalt der Perilymphe von Otosklerosefallen an alkalischer Phosphatase Glukose und Proteine (schwarze Saulen), verglichen mit den normalen Durchschnittswerten dieser Stoffe in der menschlichen Perilymphe, im Liquor cerebrospinalis und im Blutserum

Abb 3 Haufigkeitsverteilung von Na^+ K^+ und Cl^- in der Perilymphe von Otosklerosefallen

b) Gehalt an alkalischer Phosphatase, Glukose und Proteinen

Die Abb 2 gibt in derselben Darstellung Auskunft uber den durchschnittlichen Gehalt an *alkalischer Phosphatase* (in Bodansky E), an *Glukose* (in mg/l) und an Proteinen (*in mg%*) *in der* normalen Perilymphe, im *Liquor* und im Serum (*weisse Säulen*), in der *Otosklerose* Perilymphe (schwarze Säulen) Fur die Glukose fehlen die *zum* Vergleich benötigten Angaben uber den normalen Gehalt in der *menschlichen Perilymphe*

Wir messen in der *Perilymphe* unserer Otosklerosefälle einen Durchschnittswert von 70 mg% Glukose

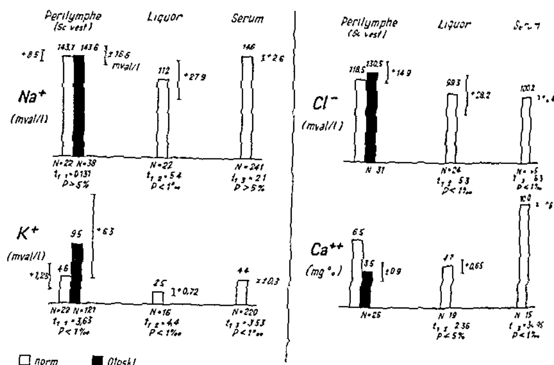


Abb. 1. Der durchschnittliche Gehalt der Perilymphe von Otosklerose-Fällen an Na^{+}, K^{+}, Cl^{-} und Ca^{++} (schwarze Säulen), verglichen mit den normalen Durchschnittswerten dieser Elektrolyte in der menschlichen Perilymphe, im Liquor cerebrospinalis und im Blutserum.

Kolonne sind zum Vergleich die entsprechenden Elektrolytwerte im normalen Liquor cerebrospinalis und im normalen Blutserum aufgeführt. Die schwarzen Säulen in der 1. Kolonne geben den durchschnittlichen Gehalt an Elektrolyten in der Perilymphe von *N* Otosklerosefällen an.

Die Streuung des Durchschnittes (*S*) ist als +/−-Wert angegeben. *N* entspricht der Zahl der untersuchten Fälle. Unter den Säulen wird als *t* der Wert für die Signifikanz des Unterschiedes zwischen Perilymphresultat und Liquor- und Serumresultat bezeichnet. Die dazu verwendeten *n*- und *P*-Werte sind in Klammern unter dem *t*-Wert angegeben.

Für Na^{+} und Cl^{-} finden sich keine signifikanten Unterschiede zwischen den normalen Perilymphwerten und den Perilymphwerten in Otosklerosefällen. Dagegen ist der *Durchschnittswert für K^{+} in der Perilymphe von Otosklerosefällen gegenüber der Norm-* und gegenüber dem Liquor und dem Serum *signifikant erhöht.* Die Streuung ist mit ±6,3 sehr gross. Der Durchschnittswert für Ca^{++} gegenüber dem von Rauch angegebenen Durchschnittswert ist deutlich erniedrigt.

* Als Norm sind die Werte eingetragen, welche S. Rauch angibt. Ein statistischer Vergleich dieser Angaben mit unseren Werten ist nur in jenen Bestimmungen von Rauch möglich, in denen dieser Autor neben den Durchschnittswerten *Standardabweichung und* Anzahl der untersuchten Fälle angibt (K^{+}, Na^{+} und alkalische Phosphatase).

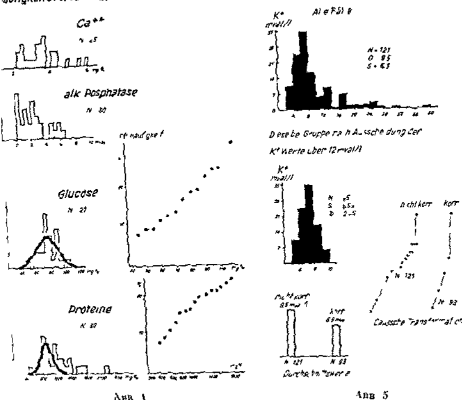


Abb. 4 Abb. 5

Abb. 4. Häufigkeitsverteilung von Ca^{++}, alkalischer Phosphatase, Glukose und Proteinen in der Perilymphe von Otosklerosefällen.
Abb. 5. Kann aus der gefundenen Verteilung der K^+-Werte in der menschlichen Perilymphe eine homogene Gruppe gefunden werden?

Die Ca^+-Werte und die *alkalischen Phosphatase*-Werte *sind ganz* unhomogen verteilt, so dass sich die Prüfung der Normalität erübrigt.

Die Verteilung der *K^+-Jonen* ergibt *eine schief* abfallende Gausssche Normalverteilung zweiter Art. Aber nach der *Transformation* der Merkmalskala in logarythmischer Einteilung fallen sämtliche Werte über 16 mval/l ausserhalb der oberen Verteilungsgrenze.

Die Proteine ergeben ebenfalls keine *homogene* Häufigkeitsverteilung. Diese wird erst erreicht, *nachdem* die Werte über 1000 mg% unberücksichtigt bleiben.

Das *unhomogene Verhalten* dieser Wertverteilungen wird noch deutlicher, wenn die Prozentwerte in einem *Gaussschen* Wahrscheinlichkeitsnetz mit logarythmischer oder normaler *Abszisse* eingetragen werden. Bei dieser Gaussschen Transformation *liegen im Fall* einer Normalverteilung sämtliche errechneten *Punkte auf einer Geraden*. Das trifft in unserem Fall zu für das Na^+ (mit Ausnahme von 2 Extremwerten), für das Cl^- und für die

TABELLE 2

	Perilymphe			
	Norm[a]	Otosklerose	Liquor	Serum[b]
Na^+ mval/l	143.1 ± 8.[illegible]	11[illegible] ± 10.6	112 ± [illegible]	[illegible]
K^+ mval/l	4.6 ± 1.[illegible]	*9.[illegible] ± 6.3*	2.[illegible] ± 0.[illegible]	[illegible] 3
Cl^- mval/l	118.[illegible]	130.[illegible] ± 11.[illegible]	[illegible]3 ± [illegible].2	[illegible] ± 2.4
Ca^{++} mg %	[illegible]5	*3.[illegible] ± 0.9*	4.1 ± 0.[illegible]	10.0
Alk. Phosph. B. E.	0	*3.4 ± 1.83*	0.[illegible] ± 0.[illegible]	3.1+
Glucose mg %	?	74 ± 14	35 ± 14	[illegible]
Proteine mg %	70–100	*965 ± 430*	18 ± 21	[illegible]

[a] Die Normwerte für die menschliche Perilymphe sind aus der Arbeit [illegible] Rauch (*Biochemie des Hörorgans*, Verlag G. Thieme, Stuttgart 1964) entnommen.

[b] Die Serum-Werte für Na, K, Cl und Ca sind aus Angaben [illegible] J. R. [illegible] und T. S. Danowski (*The Body Fluids*, Williams & Wilkins Comp., Baltimore 19[illegible]) entnommen.

In der Perilymphe des Pferdes findet Casorati post mortem 70 mg% Glukose, während Konde in der Perilymphe des Kaninchens 220 mg% feststellt.

Wiederum sind in der otosklerotischen Perilymphe durchschnittlich 3.4 *B. E. alkalische Phosphatase* vorhanden, während *normalerweise die Phosphatase fehlt*.

Die Perilymph-Phosphatase dieser Otosklerosefälle und die Serumphosphatase sind ungefähr gleichwertig, aber die Streuung der Perilymphphosphatase (1.83 : 0.77) ist fast dreimal so hoch wie die Streuung der Serumphosphatase.

Bemerkenswert erscheint schliesslich eine deutliche *Zunahme der Proteine* in der *Perilymphe* der Otosklerosefälle.

In der Tab. 2 sind die gewonnenen Durchschnittswerte tabellarisch zusammengestellt. Die in den Otosklerosefällen erhöhten Durchschnittswerte für K, alkalische Phosphatase und Proteine werden durch Schrägschrift hervorgehoben.

c) Häufigkeitsverteilung der gefundenen Werte

Die Abb. 3 orientiert über die Häufigkeitsverteilung der Elektrolytwerte Na, K, Cl und die Abb. 4 über die Einzelwerte des Ca, der alkalischen Phosphatase, der Glukose und der Proteine in der Otosklerose-Perilymphe.

Auf der Ordinate wird die Anzahl der Fälle und auf der Abszisse der Gehalt an dem entsprechenden Stoff angegeben. Wenn die Zahl der Fälle im Verhältnis zum Stoffgehalt einheitlich verteilt ist, dann ergibt sich eine Gausssche Normalverteilung der ersten oder der zweiten Art.

Aus der Verteilung der schwarzen Säulen im Verhältnis zur gestrichelten Kurve erkennt man, dass sich die Anordnung der Werte von *Na*, *Cl* und *Glukose* einer Gaussschen Kurve der Normalverteilung annähert.

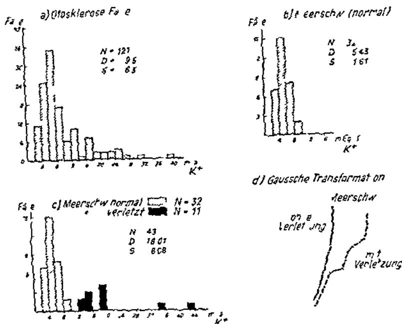


Abb. 6. Veränderung der Verteilung der K+-Werte in der Perilymphe des Meerschweinchens nach Eröffnung des Endolymphraumes

b) illustriert die Gausssche Normalverteilung der K+-Werte, welche aus der Perilymphe von 32 normalen Meerschweinchen gewonnen worden sind. Die Verteilung gleicht sehr der K+-Verteilung des otosklerosekranken Menschen, nachdem die Werte über 12 mval/l weggelassen worden sind.

c) Wir haben nun bei 11 Meerschweinchen nach der Eröffnung des ovalen Fensters den Endolymphraum verletzt und danach Perilymphe zur mikrochemischen Untersuchung entnommen. Diese Verletzungen sind später histologisch verifiziert worden. In der Abb. 7 ist eine Verletzung des Utriculus sichtbar, der Sacculus ist intakt. Nach der Verletzung des endolymphatischen Raumes findet sich in der Meerschweinchenperilymphe eine Verteilung der K+-Werte, welche der Verteilung der menschlichen K+-Werte nach der Stapedektomie sehr ähnlich ist.

d) Nach der Gaussschen Transformation ergeben die K+-Werte, welche aus der Perilymphe normaler Meerschweinchen ohne Verletzung des endolymphatischen Raumes gewonnen worden sind, eine Gerade. Sobald jedoch die Fälle mit beabsichtigter Eröffnung des Endolymphraumes miteinbezogen werden, erhält man nach der Gaussschen Transformation eine mehrfach geknickte Linie, was für das Vorliegen von mindestens drei Populationen spricht.

Im menschlichen Ohr kann eine Eröffnung des Endolymphraumes auch bei bester Technik eintreten in den nicht allzu seltenen Fällen mit bindegewebigen Strängen zwischen Utriculus und Stapesfussplatte (Abb. 8).

Glukose. Demgegenüber ergibt die Gausssche Transformation für die Verteilung der K^+-Werte eine gebrochene Linie. Es sind demnach mindestens zwei verschiedene Populationen in der Streuung der K^+-Werte enthalten. Das gleiche kann von den Proteinen gesagt werden. Die Proteine weisen eine Abknickung der Gaussschen Geraden bei 1000 mg% auf. Wegen der schon erwähnten unhomogenen Streuung der Ca^{++}- und der Phosphatasewerte erübrigt sich für diese Stoffe die Gausssche Transformation.

Diskussion der Resultate

An einer grösseren Untersuchungsgruppe *bestätigt* sich also das schon bekannte Auftreten von *alkalischer Phosphatase* in der Perilymphe von Otoskleorosefällen. Wir möchten der Annahme von Wullstein und Mitarb. beipflichten, wonach die alkalische Phosphatase aus dem otosklerotischen Knochenprozess stammt. Otoskleroseherde können die endostale Labyrinthkapsel durchsetzen. An dieser Stelle wird der otosklerotische Knochen direkt von der Perilymphe umspült.

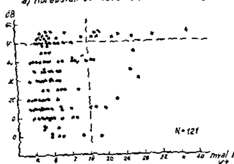
Die Erniedrigung der Ca^{++}-Werte und ihre unregelmässige *milde Verteilung* in der Perilymphe von Otoskleorosefällen hängt wahrscheinlich ebenfalls mit dem otosklerotischen Umbau in der Nachbarschaft des Perilymphraumes zusammen.

Unseres Wissens erstmals wird in der Perilymphe von Otoskleorosefällen eine *signifikante Vermehrung* des durchschnittlichen *K^+-Gehaltes* festgestellt. Wullstein, Rauch und Mitarb. haben in 1 unter 22 Stapedektomien ebenfalls eine K^+-reiche Flüssigkeit gewonnen und sie nehmen an, dass es sich dabei um Endolymphe handelte, welche infolge einer ungewollten Verletzung bzw. Eröffnung des Endolymphraumes aspiriert worden ist. Die Frage einer zufälligen *Eröffnung des Endolymphraumes* im Verlauf einer Stapedektomie muss deshalb im Hinblick auf die durchschnittliche signifikante Erhöhung des K^+-Gehaltes in der Perilymphe sorgfältig geprüft werden.

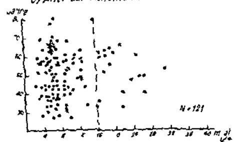
In der Abb. 5 wird untersucht, ob aus der gefundenen Verteilung der K^+-Werte in Otoskleorosefällen eine einheitliche Gruppe gefunden werden kann. Zu diesem Zweck werden alle K^+-Werte über 12 mval/l ausgelassen. Danach ergeben die übriggebliebenen Säulen eine für eine Normalverteilung typische Gausssche Kurve. Die Gausssche Transformation zeigt, dass nach Weglassung der K^+-Werte über 12 mval/l aus den zwei Linien der gemischten Population eine gerade Linie entsteht. Der ursprüngliche K^+-Durchschnittswert von 9 mval/l sinkt nach Weglassen der hohen Werte auf den Durchschnitt von 6,5 mval/l.

Die Abb. 6 zeigt, dass die nach einer Stapedektomie in der Perilymphe festgestellten erhöhten K^+-Werte möglicherweise auf eine operative Verletzung des Endolymphraumes zurückzuführen sind.

Sub a) wird die Verteilung der K^+-Werte in der menschlichen Perilymphe nach der Stapedektomie nochmals dargestellt.



dB			X^2	p	
60–50	14	9	13.8	< 1%	Abweichung gesichert
50–40	12	1	0 6	> 5%	nicht gesichert
40–30	21	3	0 3	> 5%	
30–20	16	1	0 6	> 5%	
20–10	21	3	0 3	> 5%	
10–0	17	0	2 3	> 5%	
0	4	1	0		
	16	40	17 9	< 1%	gesichert



Jahre					
80–70	3	0	0		nicht gesichert
70–60	23	6	1 2	> 5%	
60–50	30	6	0 2	> 5%	
50–40	24	3	4 3	> 5%	
40–30	22	4	0		
30–	5	0	3 3	> 5%	
	16	4	40 5 0	> 5%	

Abb. 10. a) Korrelation zwischen dem *durchschnittlichen* K+ Gehalt *in der Perilymphe* von Otoskleroseställen und dem praeoperativen Hörverlust, gemessen über die Knochenleitung für 4000 Hz b) Korrelation zwischen dem K+ Gehalt in der Perilymphe von Otoskleroseställen und dem Alter

Wenn die Erhöhung der K+-Werte in der *Perilymphe* von *Otosklerose*-fällen tatsächlich durch derartige *Verletzungen* verursacht wird, dann sollten hohe K+-Werte vor allem in den chirurgisch schwierigen Fällen mit *stark verdickter* Fussplatte und entsprechend hohem Risiko einer *Innenohr*-schädigung vorkommen. Wir haben diese Fälle an Hand des *Operations*-berichtes bestimmt und schwarz in die weissen K+ Säulen *eingetragen* (Abb. 9). Überraschenderweise ergibt sich dabei nicht die *erwartete* Häufung der chirurgisch schwierigen Fälle im Bereich *der hohen* K+-Werte, sondern eine ganz gleichmässige Verteilung. Die *grösste Anzahl* von schwierigen (schwarzen) Fällen liegt *im Bereich* der K+-Durchschnittswerte 4–12 mval/l. *Nach diesem Verteilungsbild* besteht *keine Beziehung* zwischen den *erhöhten* K+-Werten und der *Operationsschwierigkeit* bzw. dem höheren Risiko einer Eröffnung des Endolymphraumes. Deshalb *muss eine* weitere Möglichkeit der K+-Erhöhung mit in Betracht *gezogen* werden, die Möglichkeit, dass das K+ in der Perilymphe *schon vor der Stapedektomie* vermehrt vorhanden ist.

Zur Abklärung dieser Frage *untersuchen* wir in der Abb. 10 die statistische Korrelation *zwischen der Innenohrfunktion* und dem K+-Gehalt der Perilymphe.

Als Mass der peripheren Schallperzeption wird unter a) der praeoperative *Wert der Knochenleitung* bei *4000 Hz* gewählt, *weil in* diesem besonders

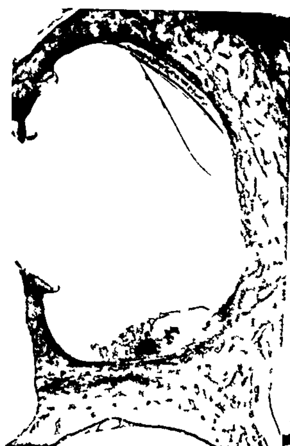


Abb. 7



Abb. 8

Abb. 7. Experimentelle Verletzung des Utriculus beim Meerschweinchen nach Stapedektomie.

Abb. 8. Bindegewebige Verbindungen zwischen dem Utriculus und der Stapesfussplatte beim Menschen.

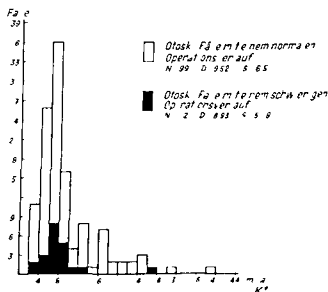


Abb. 9. Verteilung der K-Werte in der Perilymphe von Otosklerosefällen (weisse Säulen). Verteilung der chirurgisch schwierigen Fälle (schwarze Säulen).

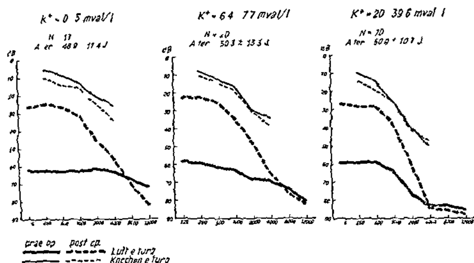


Abb. 11 Praeoperative und postoperative Durchschnittsaudiogramme von 3 Gruppen mit verschiedenen K+ Durchschnittswerten in der Perilymphe von Otosklerosefallen

sich in den Otosklerosefallen in 28,8% ein praeoperatives Vestibularis-symptom In 15,4% dieser vestibularen Storungen handelt es sich um einen Spontannystagmus und in 13,4% um einen richtungsbestimmten Lagenystagmus In keinem Fall ist ein richtungswechselnder oder regelloser Lagenystagmus vorhanden Wir sind uns bewusst, dass das so haufige Vorhandensein von diskreten praeoperativen Vestibularsymptomen in Otoskle

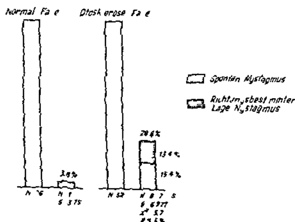


Abb. 12 Haufigkeit eines vestibularen Symptoms bei normalen ohrgesunden Versuchspersonen und in Otosklerosefallen (prae-op)

empfindlichen Bereich die grössten Hörunterschiede vorhanden sind (Die Ordinate zeigt in Decibel den praeoperativen Hörverlust für die Knochenleitung bei 4000 Hz. Auf der Abszisse sind die in der Perilymphe festgestellten K^+-Werte in mval/l angegeben.) Schon bei der groben Übersicht fällt auf, dass die Hörverluste im Bereich der hohen K^+-Werte unregelmässig verteilt und besonders zahlreich sind. Wenn man zur statistischen Auswertung eine Linie zieht zwischen den Werten, die unterhalb von 16 mval/l und oberhalb davon liegen, dann ergibt sich auf der sogenannten Mehrfeldertafel eine signifikante Abweichung, die für diejenigen Fälle, welche über −30 dB liegen, besonders stark ausgeprägt ist.

(Die Wahrscheinlichkeit, mit dieser Aussage einen Fehler zu begehen, ist für alle Gruppen zusammen kleiner als 1%; für die Werte, die oberhalb −30 dB liegen kleiner als 1‰.)

In bezug auf diese statistisch nachweisbare Korrelation zwischen Hörverlust und hohem K^+-Gehalt der Perilymphe könnte der Einwand erhoben werden, dass für die asymmetrische Verteilung der Hörverluste eine asymmetrische Aufteilung des Alters der untersuchten Patienten verantwortlich sei. Zur Prüfung dieses Einwandes wird unter b) die Korrelation zwischen dem Alter der Otosklerosefälle (in Jahren auf der Abszisse) zu den K^+-Werten der Perilymphe (in mval/l auf der Ordinate) dargestellt. Dabei erkennt man, dass sich das Alter gleichmässig über sämtliche K^+-Kategorien verteilt. Auch die Auswertung an Hand der Mehrfeldertafel zeigt, dass für keinen K^+-Wert ein signifikanter Unterschied in der Altersverteilung nachgewiesen werden kann.

Um die Beziehung zwischen Innenohrfunktion und den K^+-Werten in der Perilymphe besser zu veranschaulichen, werden in der Abb. 11 die Durchschnittsaudiogramme von drei Gruppen von Otosklerosefällen aufgezeichnet. Eine erste Gruppe enthält 17 Fälle mit einem K^+-Gehalt von 0–5 mval/l. Eine zweite Gruppe umfasst 20 Fälle mit einem K^+-Gehalt zwischen 6,4 und 7,7 mval/l. In der dritten Gruppe befinden sich 10 Fälle mit einem extrem hohen K^+-Wert von 20–39 mval/l. Der Vergleich der Knochenleitung zeigt schon vor der Operation in der Gruppe mit hohen K^+-Werten einen grösseren Hörverlust im Bereich der oberen Tonfrequenzen. Wie in der dünngestrichelten Kurve erkennbar ist, tritt nach der Stapedektomie auch in der dritten Gruppe der hohen K^+-Werte keine wesentliche Verschlechterung der Knochenleitung ein. Diese Tatsache spricht nicht unbedingt gegen eine Verletzung des Innenohrs, doch macht sie diese Annahme immerhin weniger wahrscheinlich.

Um eventuelle Korrelationen zwischen dem K^+-Gehalt der Perilymphe und den Funktionen des Vestibularapparates abzuklären, wird in der Abb. 12 an Hand von Elektronystagmogrammen die Häufigkeit von vestibulären Symptomen in einer Gruppe von 26 normalhörenden Personen mit einer Gruppe von 52 Otosklerosefällen vor der Operation verglichen. Während in den Normalfällen nur in 3,8% ein Nystagmus feststellbar ist, findet

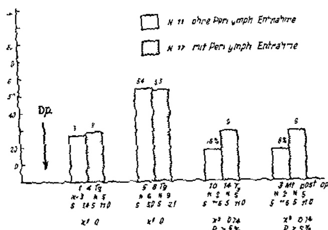


Abb 14 Vergleich zwischen dem Auftreten und dem Verlauf der postoperativen Vestibularisstörung in Otoskleroseфällen ohne praeoperative vestibuläre Symptome und ohne Perilymphentnahme (weisse Säulen) mit Perilymphentnahme (schwarze Säulen)

über 3 Monate registriert und mit den vestibulären Störungen von 17 Fällen mit Perilymphentnahme verglichen Dabei kann zwischen den beiden Gruppen kein signifikanter Unterschied in der Häufigkeit und im Verlauf der vestibulären Störungen beobachtet werden

Um endlich zu prüfen, ob eine Beziehung zwischen dem K+ Gehalt der Perilymphe und der postoperativen Vestibularisstörung vorliegt, teilen wir in der Abb 15 unsere 41 Fälle in 2 Gruppen ein 6 Fälle haben einen Kaliumgehalt der Perilymphe über 16 mval/l In 35 Fällen liegt der K+ Gehalt der Perilymphe unter 16 mval/l Die statistische Berechnung zeigt, dass in keinem Fall ein signifikanter Unterschied in der Häufigkeit und im Verlauf der vestibulären Störung vorhanden ist

Schliesslich stellen wir erstmals eine Erhöhung des Proteingehaltes in der Otosklerose Perilymphe fest Dabei stützen wir uns auf einen Normalwert (70-100 mg%), welcher von S Rauch angegeben wird

Laut einer mündlichen Mitteilung von Neiger liegt der Proteindurchschnitt im normalen Affenohr (bestimmt nach Ultra Mikro Kjehldal) höher 1712 35 + 216 mg%) Dieser Durchschnittswert stimmt mit unserem im Otosklerose-Ohr erhobenen Wert (705,2 + 185 mg%) überein, sofern alle Ergebnisse über 1000 mg% nicht berücksichtigt werden Die in unseren Fällen auffallend grosse Streuung der Proteinwerte wird von Neiger auch in Affenohren beobachtet Dass es sich dabei nicht um methodische Fehler handeln kann, beweisen die geringen Schwankungen des Proteingehaltes bei wiederholter Bestimmung in derselben Perilymphe

Die Ursache der otosklerotischen Proteinvermehrung ist unbekannt Wie

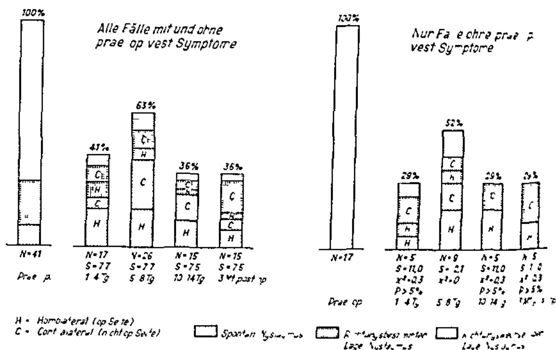


Abb 13 Ergebnis der postoperativen Vestibularisprufung in Otoskleroscfallen nach Perilymphentnahme

rosefallen mit den meisten diesbezuglichen Literaturangaben nicht ubereinstimmt. Dabei handelt es sich allerdings in der Regel um Beobachtungen ohne und mit Frenzelbrille und nicht um eine Elektronystagmographie Nur L. B W Jongkees und J Hulk finden mit Hilfe der Cupulometrie in den meisten Otoskleroscfällen eine Abweichung von der Norm. Unter Verwendung der Elektronystagmographie fanden dagegen G Aschan, M. Bergstedt und J Stahle in einem Otosklerosefall einen praeoperativen Nystagmus R Reinecken fand in 25 % der otosklerotischen Patienten vor der Operation einen Spontannystagmus und in einem Fall einen richtungsbestimmten Lagenystagmus

Die Abb 13 gibt Auskunft uber die postoperative Vestibularisprüfung in 41 Otosklerosefallen mit Perilymphentnahme im Verlauf von 3 Monaten post operationem Daneben sind aus dieser Gruppe die entsprechenden Vestibularisresultate von 17 Fallen aufgefuhrt, in welchen praeoperativ kein Nystagmus gefunden worden ist Man erkennt auf den ersten Blick, dass das Auftreten und der Verlauf der postoperativen Vestibularisstörungen nicht beeinflusst wird durch die praeoperativ schon vorhandenen Vestibulariszeichen, was auch durch die statistische Auswertung bestätigt wird

Weitere interessante Einzelheiten des postoperativen Nystagmus werden in einer besonderen Arbeit behandelt

Nun konnte die Perilymphentnahme als solche eine besondere vestibuläre Reizung auslösen Deshalb werden in der Abb 14 in den weissen Säulen die postoperativen Storungen bei 11 Patienten ohne Perilymphentnahme

Durchschnitts Audiogramme von 2 Otosklerose-Gruppen
mit einem Proteingehalt unter und über 1000 mg%

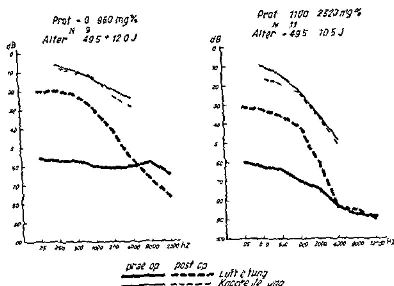


Abb. 17. Praeoperative und postoperative Durchschnittsaudiogramme von 2 Gruppen von Otosklerosefällen mit einem Proteingehalt unter und über 1000 mg%.

Beim Kaltum prüfen wir die Korrelation zwischen dem erhöhten *Proteingehalt* der Otosklerose-Perilymphe und den Innenohrfunktionen.

In der Abb. 16 wird an Hand der „2 mal 2 Felder"-Tafel die Beziehung zwischen dem Proteingehalt der Perilymphe und dem praeoperativen über Knochenleitung gemessenen Hörausfall bei 4000 Hz ausgewertet. Dabei kann ein statistisch gesicherter Hörausfall von über −40 dB bei sämtlichen Fällen mit mehr als 1000 mg% Proteingehalt der Perilymphe nachgewiesen werden. Die Möglichkeit, dass dieser Unterschied durch das *Alter der Patienten* vorgetäuscht wird, kann an Hand der *in dieser Abbildung* ebenfalls enthaltenen *weiteren „2 mal 2 Felder"-Tafel* ausgeschlossen werden.

Die Abb. 17 *enthält* die prae- und postoperativen Durchschnittsaudiogramme der *Otosklerosefälle* mit einem Proteingehalt der Perilymphe unter und über 1000 mg%. *Der stärkste Hörverlust* im Bereich der Töne hoher Frequenzen in den *eiweissreichen* Fällen ist deutlich sichtbar. Demnach darf eine *Korrelation* zwischen erhöhtem *Proteingehalt der Perilymphe* und dem praeoperativen, über Knochenleitung *gemessenen Hörausfall* bei 4000 Hz als statistisch gesichert bezeichnet werden.

Demgegenüber *gelingt es vorläufig nicht (Abb. 18)*, eine Korrelation zwischen der Eiweissvermehrung *in der Perilymphe* und den Vestibularisstörungen nachzuweisen. 7 Fälle *mit einem* Proteingehalt unter 1000 mg% zeigen praeoperativ einen Nystagmus, *in 5* Fällen mit einem Proteingehalt über 1000 mg% ist kein *praeoperativer* Nystagmus nachweisbar. Postopera-

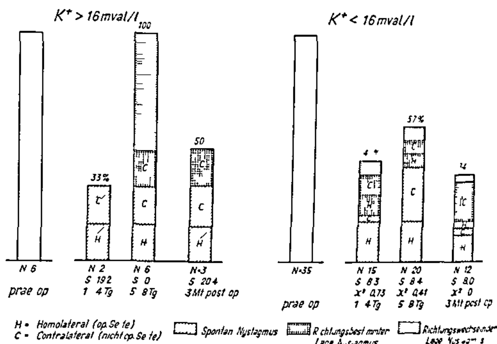
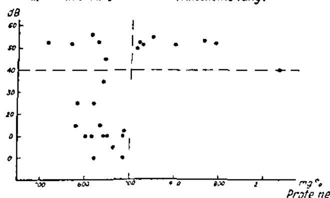


Abb. 15. Auftreten und Verlauf der postoperativen Vestibularisstörung in Otosklerosefällen mit einem K⁺ Gehalt der Perilymphe unterhalb und oberhalb von 16 mval/l



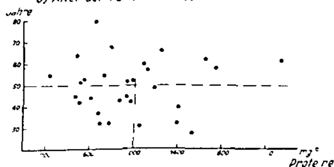


Abb. 16. a) Korrelation zwischen dem Proteingehalt der Perilymphe von Otosklerosefällen und dem präoperativen Hörverlust, gemessen über die Knochenleitung bis 4000 Hz. b) Korrelation zwischen dem Alter der Fälle und dem Proteingehalt der Perilymphe

RÉSUMÉ

Chez 155 otosclérotiques la périlymphe a été prélevée au cours d'une stapédectomie. Le taux du potassium, sodium, chlore, calcium, phosphatase alcaline, glucose et protéine a été déterminé en 302 analyses.

La présence de phosphatase alcaline dans la périlymphe des malades otosclérotiques a été confirmée. Les valeurs du calcium sont en moyenne diminuées et présentent une distribution irrégulière. Une augmentation statistiquement significative du taux moyen du potassium et du taux moyen des protéines est observée et son origine est discutée. Une corrélation entre l'augmentation du potassium et des protéines d'un part et la perte auditive préopératoire (mesurée par conduction osseuse) de l'autre part est démontrée. Par contre une conclusion entre l'augmentation du potassium et des protéines d'un coté et des troubles vestibulaires pré- et postopératoires d'autre part n'est pas trouvée.

LITERATUR

ANCHAN, G., BERGSTEDT, M. und STAHLE, J., 1956. Nystagmography. *Acta Otolaryng. (Stockh.)*, Suppl. *129*.

CASORATI, V., 1958. Su di alcune caratteristiche fisiche a chimiche della perilinfa e del liquor del cavallo. *Clin. Otorinolaring.* *10*, 398.

CITRON, L., EXLEY, D. und HALLPIKE, C. S., 1956. Formation, circulation and chemical properties of the labyrinthine fluids. *Brit. Med. Bull.*, *12*, 101.

CROSBY, W. H. und FURTH, F. W., 1956. *Blood* 11, 380.

HILK, G. und JONGKEES, L. B. W., 1950. Vestibular examination in cases of otosclerosis. *J. Laryng.* *64*, 126.

HULTMAN, E., 1959. *Nature* *183*, 108.

HYVÄRINEN, A. und NIKKILÄ, E., 1962. *Clin. Chim. Acta* *7*, 140.

KOIDE, Y., 1958. Introductory studies on the chemical physiology of the labyrinth. *Acta Med. Biol.* *6*, 1.

RAUCH, S., 1964. *Biochemie des Hörorgans.* Thieme, Stuttgart.

REINECKEN, R., 1960. Vestibularisuntersuchungen nach Operationen am ovalen Fenster. *Z. Laryng. Rhinol. Otol.* *39*, 432.

SANZ, M. C., 1957. Ultramicromethods and standardization of equipment. *Clin. Chem.* 3, 406.

1959. Physico-chemische Grundlagen und apparative Neuentwicklungen in der quantitativen Ultramikroanalyse. *Chimia* *13*, 192.

SMITH, C. A., LOWRY, O. H. und WU, M. L., 1954. The electrolytes of the labyrinthine fluids. *Laryngoscope* *64*, 141.

WELLSTEIN, H. L., KLEY, W., RAUCH, S. und KOSTLIN, A., 1960. Zur Biochemie der Perilymphe operierter Otosklerosen. *Z. Laryng. Rhinol. Otol.*, *39*, 665.

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DISCUSSION

H. Mittermaier: Herrn Ruedi möchte ich fragen, ob er Gelegenheit gehabt hat, bei den audiologischen Untersuchungen der Otosklerose-Patienten auch Fälle

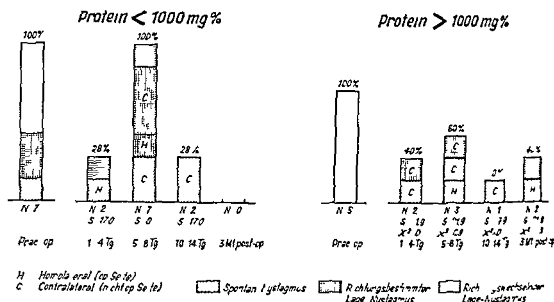


Abb. 18. Auftreten und Verlauf einer vestibulären Störung in Otosklerosefällen mit einem Proteingehalt der Perilymphe unter- und oberhalb 1000 mg%.

tiv tritt in beiden Gruppen ein ähnliches Nystagmusbild auf, das in typischer Weise abklingt. Obwohl in beiden Gruppen die Anzahl der untersuchten Fälle klein ist, zeigen die Resultate keinen signifikanten Unterschied.

Weitere Untersuchungen über den Proteingehalt der Perilymphe in Otosklerosefällen, im Zusammenhang mit der Messung der prae- und postoperativen Schallperzeption und der prae- und postoperativen Vestibularisfunktion erscheinen notwendig.

SUMMARY

In 155 otosclerotic patients perilymph has been collected in the course of a stapedectomy. The concentration of potassium, sodium, chloride, alk. phosphatase, glucose and proteins present in the collected perilymph has been determined in 302 samples.

The presence of alk. phosphatase in the perilymph of otosclerotic patients is confirmed. The calcium values are lower than normal and irregularly distributed. The average concentration of potassium and proteins is found in the perilymph of otosclerotic patients to be increased over normal values. The cause of the increased potassium concentration is discussed. A correlation between the increased potassium and protein values and the preoperative hearing impairment for the bone conduction at 4000 cps is statistically proved. However no statistical correlation is evident between the increased potassium and protein values and the pre- or postoperative vestibular symptoms of otosclerotic patients.

VERGLEICHENDE BESTIMMUNG EINIGER ELEKTROLYTE UND ORGANISCHER SUBSTANZEN IN DER PERILYMPHE OTOSKLEROSEKRANKER PATIENTEN

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(Dir. Prof. Dr. H. L. Wullstein)

Eine vergleichende Bestimmung der Konzentration von Na^{+}, K^{+}, Ca^{2+} und PO_4^{3-}-Ionen und von Glukose, Cholesterin, Protein und LDH-Aktivität im Serum, Liquor und in der Perilymphe des Menschen ergibt, dass Perilymphe mit Wahrscheinlichkeit als Plasmafiltrat angesehen werden kann. Die Perilymphe Otosklerosekranker hat wahrscheinlich einen anderen K^{+}- und PO_4^{3-}-Gehalt als die von Patienten mit altersentsprechendem normalen Audiogramm. Zwischen Glukose- bzw. Proteingehalt und Innenohrleistung ist noch keine Beziehung zu erkennen.

Die Frage nach der Entstehungsart der Perilymphe ist bisher noch nicht endgültig geklärt. Viele Autoren sind der Meinung, es handle sich um ein Ultrafiltrat des Plasmas. Hauptstützen dieser Ansicht sind zwei Tatsachen. Die Perilymphe ist gegenüber dem Plasma wesentlich proteinärmer und es wurden bisher noch keine sekretorisch aktiven Zellen im Bereich der Perilymphwände histologisch nachgewiesen. Dennoch konnte sich diese vor allem auf indirekten und qualitativen Beweisen beruhende Hypothese nicht recht durchsetzen gegenüber gewichtigen Argumenten, die der Endolymphe oder dem Liquor einen massgeblichen Anteil an der Perilymphproduktion zusprachen.

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Insgesamt wurden 132 Human-Perilymphen (davon 122 Otosklerosefälle) untersucht, die von sechs an unserer Klinik tätigen Operateuren gewonnen wurden. Proben mit einem Blutgehalt über 10% wurden verworfen.

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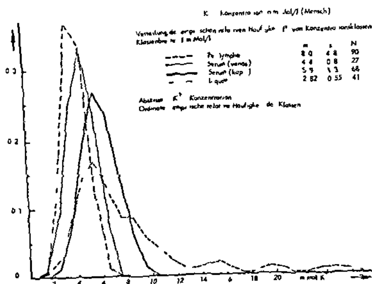


Abb 1 Verteilung der K Konzentrationsklassen und tabellarische Zusammenstellung von Mittelwert *m* Standardabweichung *s* sowie Stichprobenumfang N in Perilymphe Serum und Liquor des Menschen

wenn mit f_i die experimentell gefundene Klassenfrequenz bezeichnet wird

Kapillarserum (aus dem Ohrläppchen gewonnen) hat im Mittel eine Konzentration von 5 87 mM/l venöses Serum 4 37 mM/l und Liquor 2 82 mM/l, die Populationen sind normal verteilt (Prüfung durch χ^2 Test) Für die Human Perilymphe ergab sich ein Mittelwert von 8 01 bei asymmetrischer Häufigkeitsverteilung Vergleicht man jedoch die Häufigkeitsmaxima vom Kapillarserum und der Perilymphe so findet sich kein Unterschied Diese Übereinstimmung wird noch deutlicher, wenn man die Werte der Perilymphen unterteilt In solche mit audiometrisch normaler und solche mit schlechter Innenohrleistung Man sieht dass der auffallende Ausläufer *nach rechts in der Gesamtverteilungskurve vornehmlich in die Population* der schlechten Innenohren gehört Der Unterschied der mittleren Kalium Konzentration von Perilymphen mit normaler und schlechter Innenohrleistung lässt sich allerdings wegen der Verteilungsform statistisch nicht sichern Dabei ergibt sich eine interessante Analogie zum anorganischen Phosphat das ebenfalls im schlechten Innenohr mit 0 82 ± 0 23 mMol/l höher liegt als im normalen Innenohr mit 0 62 ± 0 14 Diese Parallelität in der Ausscheidung von K und Phosphat findet sich auch bei Stimulation der Parotissekretion beim Menschen wobei der K- und der Phosphatpegel in gleicher Weise ansteigen

Im Gegensatz zur Speichelsekretion kann im Tierversuch durch Pilocarpin weder die Perilymphproduktion noch das Ionenverhältnis verändert wer

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Begründung

1. Hinsichtlich Glucose, Cholesterin, Kalium, Natrium und freiem Calcium treten die verschiedenen Konzentrationsklassen in Perilymphe und Serum, nicht aber im Liquor mit annähernd gleicher Häufigkeit auf. Damit entsprechen sich in Perilymphe und Serum auch Mittelwert und Varianz.

2. Die wahrscheinlichsten Werte der LDH-Aktivität in der Perilymphe unterscheiden sich nicht von denen des Serums, sie sind aber wesentlich höher als die im Liquor.

3. Der mittlere Phosphatgehalt ist höher als im Liquor, wenn auch etwas niedriger als im Serum.

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Die Untersuchung ergibt weiter, dass Patienten mit audiologisch gegenüber der Norm verschlechterter Innenohrleistung wahrscheinlich eine erhöhte Kalium- und Phosphatkonzentration in der Perilymphe haben.

Letztlich deutet die Häufigkeitsverteilung der LDH-Aktivität in der Perilymphe auf Artefakte hin, die möglicherweise durch das Operationstrauma verursacht werden. Gestützt wird diese Vermutung durch Versuche beim Meerschweinchen.

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Die Bestimmungen von Na^{+}, K^{+} und Ca^{+} wurden flammenphotometrisch mit 1,8 μl Probe durchgeführt. Die messmethodischen Fehler einer Einzelmessung betragen bei K^{+} $\pm 0{,}73$ mMol/l, bei Ca^{+} 0,23 mMol/l.

Kalium

Die empirische, relative Häufigkeit der Konzentrationsklassen f' von K^{+} in Serum, Perilymphe und Liquor zeigt Abb. 1. Der Messfehler berechtigt hier und in den folgenden Darstellungen zu einer 50%igen Überlappung mit den Frequenzen der links und rechts benachbarten Klassen. Dies bedeutet, die empirische Frequenz der i-ten Klasse f_i berechnet sich nach

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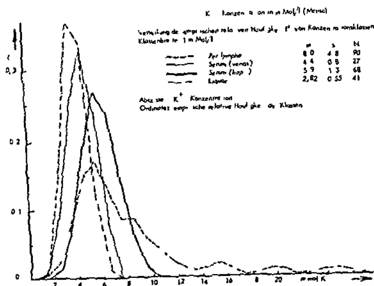


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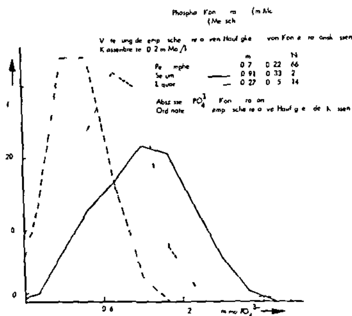


Abb. 3 Verteilung der PO₄ Konzentrationsklassen in Perilymphe Serum und Liquor und tabellarische Zusammenstellung der Ergebnisse

Phosphat

Die Konzentration wurde mit einer von Mokrasch modifizierten Methode nach Fiske-Subbarow bestimmt. Zur Bestimmung genügten 1 1 8 μl. Der methodische Fehler lag bei $\pm 0{,}05$ mMol/l

Abb. 3 zeigt die Darstellung der relativen Häufigkeit der PO_4^{3-} Konzen

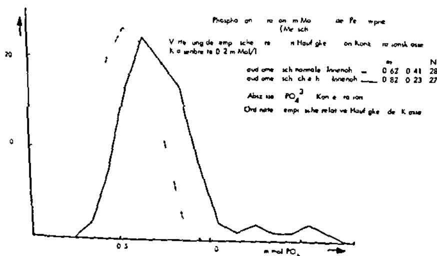


Abb. 4 Verteilung der PO_4 Konzentrationsklassen in der Perilymphe von audiometrisch gut und schlechten Innenohren

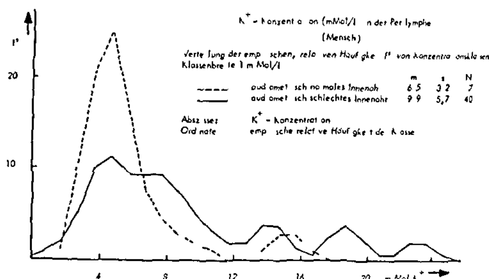


ABB. 2. Verteilung der K+-Konzentrationsklassen in audiometrisch guten und schlechten Innenohren und tabellarische Zusammenfassung der Ergebnisse

den. Daraus darf geschlossen werden, dass solche aktiven Sekretionsvorgänge hierbei nicht stattfinden.

Hinsichtlich des Natriumgehaltes lassen sich keinerlei Unterschiede zwischen Serum, Perilymphe und Liquor feststellen.

Calcium

Die Total-Ca^{2+}-Konzentration ist im Serum wesentlich höher als in Perilymphe und Liquor. Der Ca^{2+}-Gehalt der Perilymphe entspricht jedoch dem des nicht proteingebundenen Ca^{2+} im Serum. Beim Meerschweinchen zeigt sich dieser sichere Unterschied zwischen Perilymphe und Liquor nicht so deutlich.

TABELLE 1. *Calciumgehalt der Körperflüssigkeiten in mMol/l*

	m	s	N
Mensch			
Serum	1,96	0,15	24
Serum von Otosklerosekranken	1,57	0,53	13
Perilymphe	1,27	0,46	71
Liquor	0,88	0,12	11
Meerschweinchen			
Serum	2,25	0,39	1
Perilymphe (Scala tympani)	0,98	0,43	7
(Scala vestibuli)	1,04	0,55	32
Liquor	1,21	0,55	26

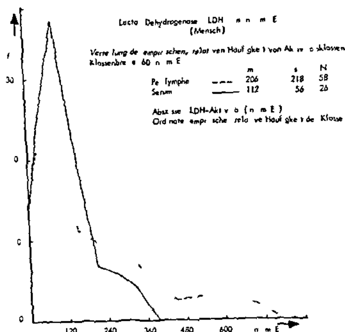


Abb. 5 Verteilung der LDH Aktivitätsklassen in Perilymphe und Serum sowie tabellarische Zusammenstellung der Ergebnisse

der wahrscheinlichsten Werte in Serum und Perilymphe sind jedoch nicht zu unterscheiden

Der extrem lange rechte Ausläufer der Häufigkeitsverteilung der LDH Aktivität in der Perilymphe lässt vermuten, dass es sich hier um Artefakte handelt, die durch Manipulation am ovalen Fenster hervorgerufen wurden

Diese Vermutung kann durch Versuche beim Meerschweinchen gestützt werden durch sukzessive Entnahme der Perilymphe aus der Skala vestibuli lässt sich in ihr ein Aktivitätsanstieg nachweisen Wird vor der Entnahme der Stapes luxiert so ist bereits der Wert der ersten Entnahme signifikant erhöht (Schneider)

Beim Menschen wurden in 12 Fällen bei fraktionierter Entnahme 8 × eine Zunahme der LDH Aktivität beobachtet Wegen der Artefaktbildung war es nicht möglich bei einem Kollektiv von Patienten mit unter der Norm schlechter Innenohrleistung einen statistisch signifikanten Unterschied gegenüber einem Normalkollektiv zu erkennen Immerhin scheint die Höhe der LDH Aktivität aus der Perilymphe operierter Ohren einen Hinweis für das Ausmass des Operationstraumas zu geben

Glucose

Glucose wurde dünnschichtchromatographisch und enzymatisch mit Glucose-Oxydase nach einem modifizierten Testansatz der Boehringer Kombination nachgewiesen

trationsklassen. Liquor weist mit 0,27 ± 0,15 mMol/l den niedrigsten Phosphat-Gehalt auf. Perilymphe hat im Mittel einen zwar signifikant niedrigeren Wert als das Serum, dennoch zeigt sich zu diesem eine grosse Ähnlichkeit. Wie beim Kalium findet sich auch hier ein Unterschied beim Vergleich der Perilymphe audiometrisch normaler und audiometrisch schlechter Innenohren. Die Unterschiede lassen sich in Abb. 4 deutlich erkennen.

Bei Stapedolyse-Operationen gibt es gelegentlich Fälle mit abnorm vermehrtem Perilymphfluss. Wird hierbei Perilymphe sukzessive entnommen, so kann in einigen Fällen eine Abnahme der Phosphat-Konzentration und ihre Angleichung an die Werte des Liquors beobachtet werden.

Protein

Die Proteine wurden mit Trichloressigsäure gefällt, gewaschen, in alkalischem Medium gelöst und mit Folinschem Phenolreagenz nachgewiesen. Es wurden 13 Humanperilymphen mit einem mittleren Blutgehalt unter 3,5‰ untersucht, der Mittelwert konnte daher um etwa 200 mg% zu hoch liegen. Die Differenz im Proteingehalt zwischen Serum und Perilymphe kann durch *Plasmafiltration* erklärt werden.

Beim Menschen fanden wir in der Perilymphe 728 mg% mit einer Standardabweichung s ±465. Zum Vergleich enthält Serum 6000–7000 mg% und Liquor 20–40 mg%. (Die Werte für Serum und Liquor sind zitiert nach Rauch.)

Von weiteren differenzierten Untersuchungen der *Human*perilymphe auf Protein wurde abgesehen, da die Entnahmetechnik zur Zeit einen sicheren Ausschluss von Verunreinigungen mit Serum und Gewebsflüssigkeit über 5‰ noch nicht gewährleistet.

Beim Meerschweinchen ist Liquor und Perilymphe bezüglich Proteingehalt nicht zu unterscheiden.

Perilymphe	227 mg% + 163	(33 Fälle)
Liquor	210 mg% + 143	(7 Fälle)

Lactat-Dehydrogenase (LDH)

Die Bestimmung geschah mit einem modifizierten Ansatz der Testkombination von Boehringer. 1 μl Probe genügte zur Bestimmung, da das Endvolumen des Testansatzes unter 30 μl lag.

Ergebnis:

Perilymphe	206 int. Millieinheiten	± 218	(58 Fälle)
Serum	112	± 56	(26 Fälle)
Liquor	0,7 (zit. n. Bruns)		

Die empirische, relative Häufigkeitsverteilung ist in Abb. 5 wiedergegeben. Da es sich in beiden Fällen um eine asymmetrische Verteilung handelt, ist es wenig sinnvoll, die Mittelwerte zu vergleichen. Die Verteilung

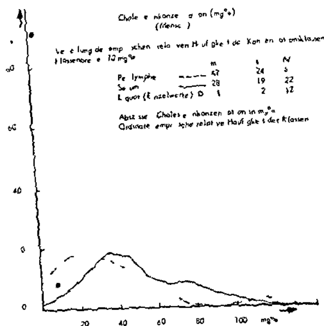


Abb. 7. Verteilung der Cholesterin-Konzentrationsklassen in Perilymphe, Serum, Liquor und tabellarische Zusammenstellung der Ergebnisse

	m (mg%)	s	N
im Serum	47	24	45
in der Perilymphe	28	19	22
im Liquor	1	2	12

Die Mittelwerte des Cholesteringehaltes in Perilymphe und Serum sind vergleichbar, auch wenn sich auf Grund dieser Stichproben mit einer Signifikanzwahrscheinlichkeit $2\alpha \begin{matrix} > 0{,}001 \\ 0{,}005 \end{matrix}$ ein Unterschied ergibt. Nahezu mit Sicherheit auszuschliessen ist jedoch eine Ähnlichkeit mit Liquor, wo sich unter 12 Proben nur eine mit messbarem Cholesteringehalt fand.

SUMMARY

The nature of origin of perilymph is not yet clarified. Many authors are thinking perilymph is an ultrafiltrate of plasma. There are two main arguments for this conception:

1. Perilymph shows only a small fraction of the protein content of the plasma,
2. Up to now there is no histological evidence for active secretion in the walls of perilymph space.

However, these two arguments fail to exclude the possibility that perilymph may originate from endolymph and liquor. Other arguments for the ultrafiltration hypothesis are rather indirect or qualitative and therefore not striking. Chemical analysis of perilymph and statistical comparison of special substances whose con

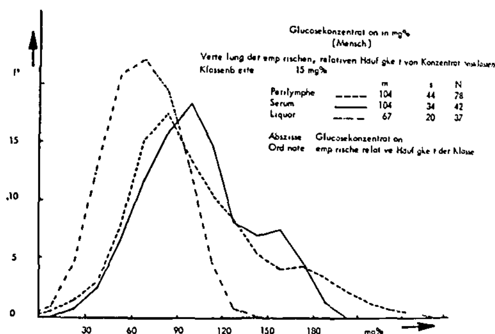


Abb. 6. Verteilung der Glucosekonzentrationsklassen in Perilymphe, Serum, Liquor und tabellarische Zusammenstellung der Ergebnisse.

Beim Menschen fand sich folgendes:

	m (mg%)	s	N
Serum	104	34	42
Perilymphe	104	44	78
Liquor	67	20	37

Die relative, empirische Häufigkeit der Klassen zeigt Abb. 6. Wie ersichtlich, lässt sich der mittlere Glucosegehalt der Perilymphe nicht von dem des Serums unterscheiden.

Neben diesem statistisch gleichartigen Verhalten zeigt sich auch funktionell eine grosse Ähnlichkeit von Serum und Perilymphe.

Beim Meerschweinchen findet man nach intraperitonealer Insulininjektion (17 Einheiten/100 g) im Serum und in der Perilymphe parallele Verläufe der Glucose-Pegel. Der Liquor-Pegel unterscheidet sich durch eine wesentlich höhere Initialzacke.

Allerdings scheint der Glucosegehalt beim Meerschweinchen im Serum höher zu liegen als in der Perilymphe, eine statistische Sicherung steht noch aus.

Cholesterin

Cholesterin wurde dünnschichtchromatographisch getrennt, mit Jod-Dampf gefärbt und photographisch quantitativ ausgewertet. Als Probemenge genügte 1 μl, der methodische Fehler des Einzelwertes betrug ± 13 mg%. Das Ergebnis veranschaulicht Abb. 7.

Beim Menschen fanden wir:

DISCUSSION

H Schuknecht The elucidation of chemical alterations attendant with and responsible for inner ear disorders undoubtedly will comprize a considerable part of our research effort in the future The excellent presentations of this morning indicate a widespread cognigance of the importance of biochemistry in the function of the inner ear It seems reasonable to assume that alterations in biochemistry of the fluids would create diffuse functional alterations, in other words in the cochlea the functional changes would involve the entire auditory spectrum This idea seems to be supported, in part at least, by the findings in 3 different otological disorders all characterized in some cases and some stages of the diseases by flat loss audiograms without structural alterations in the sensory and neural elements

(*a*) In Meniere s disease there are often flat audiometric losses with a normal organ of Corti and spiral ganglion by light microscopy and pathologically an increase in endolymph volume, which could be expected to create alteration in chemical values

(*b*) Presbycusis characterized by equal loss (flat) audiograms with normal sensory and neural elements with the only structural change (on light microscopic study) being an atrophic change in the stria vascularis

(*c*) Occasionally during the early stages of acoustic tumor there may be flat audiometric curves In such cases there may be insufficient structural change in the sensory and neural elements to explain the threshold elevations That these losses might be due to a biochemical disturbance is supported by the occasional finding of an eosinophilic precipitate in the perilymph

Whereas the treatment of inner ear disorders accompanied by structural alterations seems a formidable problem it is exciting to hope that deafness due to biochemical changes might be amenable to replacement therapy

H L Wullstein (Schlusswort) *Schuknechts* Hinweis dass die audiologischen Verluste bei Menière bei manchen Formen der Presbyakusis und bei Frühstadien von Akustikusneurinomen vielleicht einen Hinweis auf eine biochemische Schädigung über das ganze Cortische Organ als Ursache haben, ist uns wertvoll Jede Gelegenheit die sich bietet Untersuchungen nach dieser Richtung anzustellen, müssen wir nutzen Doch sind diese Gelegenheiten bei Patienten eben selten, im Tierversuche nicht einfach zu imitieren und in der biochemischen Technik kleinster Mengen vorerst noch schwierig

centration differs in liquor and serum as glucose, phosphate, lactic-acid dehydrogenase (LDH) and cholesterine may help to solve this problem. We analyzed one hundred and thirty-two specimens of human perilymph (out of these were one hundred and twenty-two of patients with otosclerosis). Samples with blood content over 10% were abolished. Perilymph of patients with healthy ears was not obtainable. We tried to manage with this handicap by dividing our total collective. The criterion was the greater or lesser disturbance of the hearing function as can be proved by audiometric measurement.

The results of our quantitative chemical investigation verify that perilymph may be considered as a filtrate of plasma in first approximation.

1. Serum and perilymph show the same frequency dispersion concerning the concentration of glucose, cholesterine, free calcium, sodium and potassium.

2. The values of maximum probability of lactic-acid-dehydrogenase activity in serum and perilymph do not differ, they are much higher than in liquor.

3. The mean phosphate concentration of perilymph is higher than in liquor and somewhat less than in serum.

4. Experiments *in guinea pigs are showing that (a)* unlike liquor the mean level of glucose in serum and perilymph after injection of Insulin run parallel, *(b)* by injection of Pilocarpine there is no significant change of potassium, calcium and phosphate concentration nor visibly increased quantity of perilymph as it should be expected in case of active secretion (for instance saliva).

Further results

Patients with audiometric impaired inner ear function show an elevated potassium and phosphate concentration level in comparison with normal ears. However, this difference is not provable statistically because of the asymmetric frequency distribution.

At last

The frequency dispersion of lactic-acid-dehydrogenase activity in the perilymph points to artificial alteration caused by the trauma of the operation. We *could confirm this hypothesis by experiments in guinea pigs.*

RESUME

Il résulte de la détermination comparative des concentrations des ions Na^{+}, K^{+}, Ca^{++} et $PO_4^{=}$ que la périlymphe des malades avec otosclérose et lésion de la fonction cochléaire montre un contenu des électrolytes différent de celui des malades avec une fonction de l'oreille interne normale ou presque normale. Aujourd'hui il n'est pas possible d'établir une relation entre la fonction cochléaire et la concentration de glucose ou bien de protéine. On met à discussion la méthode d'obtention de la périlymphe et des causes d'erreur.

LITERATUR

RAUCH, S. 1964. *Biochemie des Hörorgans.* G. Thieme-Verlag, Stuttgart.

Dokumenta Geigy — Wissenschaftliche Tabellen. J. R. Geigy AG, Basel 1960.

SCHNEIDER, E. A. 1964. Fehlermöglichkeiten bei der Lactat-Dehydrogenase-Bestimmung in der Perilymphe von Meerschweinchen. *Arch. Ohr. Nas. Kehlkopfheilk. 184,* 139–142.

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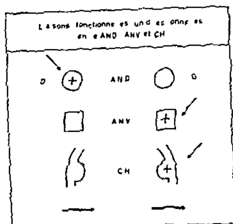


Fig. 3. AND : aires nystagmogènes diencéphaliques. ANY : aires nystagmogènes vestibulaires bulbaires. *CH* : canaux horizontaux. *d* : droite. *g* : gauche.

préciser le degré de corrélation qui pourrait exister entre certains paramètres habituels d'observation clinique et les stimulations utilisées, centrales ou périphériques.

MÉTHODE

Animal : lapin. Méthode stéréotaxique.

Dans une *première série* d'expériences, les réactions nystagmiques per- [illegible] de chaque animal sont testées au moyen de [illegible]

Une accélération angulaire choisie, entre 0,2/s² et 20°/s², se maintient rigoureusement constante du commencement à la fin (± 5%). C'est une condition fondamentale ainsi qu'une étude statistique comparative de notre matériel documentaire faite à la Faculté d'Aix-Marseille (Thèse Niccolaï Harter 1964) vient encore de le démontrer.

Les stimulations utilisées sont des accélérations angulaires s'échelonnant entre 0,5°/s² et 10°/s², d'une durée variable ou d'une durée constante.

L'enregistrement du nystagmus a lieu en chambre noire, par la méthode habituelle, au moyen d'un électroencéphalographe à courant alternatif avec une constante de temps de 0,3.

Dans une *deuxième série* d'expériences, *on met en place un dispositif* stéréotaxique au niveau de l'AND. Puis l'animal est soumis à des stimulations électriques au moyen d'un stimulateur à impulsions rythmiques rectangulaires (50 imp/s, 0,5 à 1 ms). Les stimulations, chacune d'une intensité constante, sont échelonnées entre 0,2 et 2 V, avec une durée d'application variable ou constante.

L'enregistrement du nystagmus a lieu comme précédemment. Ultérieurement, l'animal est soumis à des stimulations rotatoires de contrôle correspondant à celles de la première série.

NYSTAGMUS CENTRAL ET NYSTAGMUS PÉRIPHÉRIQUE

Étude électro-nystagmographique comparative des réponses aux stimulations expérimentales des centres nystagmogènes et des réactions giratoires per- et post-rotatoires chez l'animal (lapin)

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Les présentes recherches expérimentales font ressortir le parallélisme des réponses nystagmiques obtenues par stimulation électrique des centres diencéphaliques et par stimulation rotatoire des récepteurs vestibulaires, en ce qui concerne :

- la *latence* qui est de plusieurs secondes;
- l'*apparition* d'une *réaction nystagmique*, de rythme régulier, à secousses diphasiques, horizontales, battant dans une direction déterminée et unique, à droite ou à gauche,
- l'*existence* d'un *même seuil réactionnel*, qui est un seuil de fréquence,
- un accroissement rapide de la fréquence du nystagmus pendant la première période de la stimulation,
- l'installation d'une fréquence maxima stable dont le niveau (en H_z) s'accroît avec l'intensité de la stimulation (en °/s² ou en volts),
- l'épuisement de la réaction dans la stimulation de longue durée (80 secondes et au delà) et au contraire l'augmentation de la durée de la réponse, avec apparition de post-décharges nystagmiques, lorsque l'intensité du stimulus, électrique ou rotatoire, est augmentée (réaction inépuisable)

Une corrélation fonctionnelle entre les centres nystagmogènes diencéphaliques (AND), les centres vestibulaires bulbaires (ANV) et les récepteurs des canaux semicirculaires a été établie précédemment par les travaux de Lachmann (1958), de Monnier avec son élève Pierre Montandon (1961) et de nous-mêmes (1961). Ces différents travaux expérimentaux, auxquels nous nous référons, ont été effectués en étroite collaboration entre l'Institut de Physiologie de Bâle et notre Laboratoire.

Les liaisons fonctionnelles ainsi établies sont sommairement résumées dans le schéma suivant.

La stimulation du CHd, comme celle de l'ANVd et celle de l'ANDg, donne naissance à un nystagmus battant *à droite*.

Il en est de même pour le nystagmus battant *à gauche* qui résulte d'une stimulation du CHg, comme de celle de l'ANVg et de celle de l'ANDd.

Il nous a paru intéressant de poursuivre ces recherches en essayant de

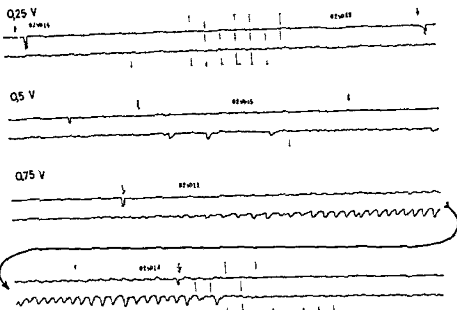


Fig. 3. Stimulations électriques stéréotaxiques de l'aire nystagmogène diencéphalique à droite à 0,25 V, 0,5 V, 0,75 V: nystagmus battant à gauche (tracé inférieur).

1) à 1°/s² de 0,5 Hz (réaction partielle infraliminaire);
2) à 3°/s², de 1,6 Hz (seuil du nystagmus);
3) à 6°/s² de 2,5 Hz;
4) à 10°/s² de 3,8 Hz.

Résultats déterminés statistiquement par la méthode des « moyennes mobiles » chez l'animal normal.)

Pour des accélérations de 3°/s² et de 6°/s², on observe une *diminution de la fréquence* à partir de la 12ème et 15ème seconde, l'accélération étant maintenue constante.

Lorsqu'on cesse l'accélération, on a pu noter, avec des accélérations de 6°/s² et 10°/s², un dépassement de la réaction nystagmique sur la période post-stimulatoire. La durée de ce dépassement semble croître avec la durée de la stimulation. Nous n'avons jamais constaté chez l'animal sain un changement de direction du nystagmus.

b) *Stimulation électrique de l'AND*

Latence: pour les stimulations utilisées, elle est de plusieurs secondes également jusqu'à l'apparition du nystagmus, dont la direction correspond au côté stimulé (à gauche pour l'AND droite et inversement). A titre d'exemple les résultats obtenus chez deux animaux, dont le seuil électrique est différent, sont les suivants:

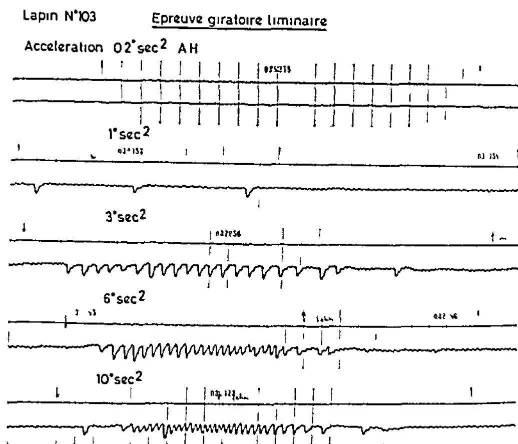


FIG. 2. Stimulations giratoires de sens antihoraire avec des accélérations de 0,2°/s², 1°/s², 3°/s², 6°/s², 10°/s², nystagmus battant à gauche.

RÉSULTATS

Les paramètres de *fréquence* et de *durée* du nystagmus ont spécialement retenu notre attention. Le nombre restreint d'animaux étudiés jusqu'ici n'a permis l'évaluation statistique que de certains paramètres. De plus, l'allure générale des résultats observés au cours de ces nouvelles recherches concorde dans l'ensemble avec celle des précédents travaux.

Analyses des réponses

a) *Épreuves rotatoires*

Au début de la rotation, après une *latence* variable, de 2 à 8 secondes, pour des accélérations comprises entre 1°/s² et 10°/s², un nystagmus apparaît dont la direction correspond au sens de la rotation. Sa *fréquence* croît très rapidement pour atteindre en quelques secondes une *valeur maximum stable*. Le niveau de ce maximum, ou « plateau fréquentiel », est d'autant plus élevé que l'intensité du stimulus rotatoire, mesurée en °/s² d'accélération angulaire, est plus forte.

Ainsi à titre d'exemple (lapin n° 103), les fréquences maxima (en H_z) observées à différentes accélérations sont:

la réaction nystagmique tout au long d'une stimulation de plus de 4 minutes, avec d'importantes fluctuations de la fréquence, sans aucune interruption et sans changement de direction, qui fut même suivi d'un dépassement de 20 s après la fin.

Dans les stimulations de *courte durée*, au dessous de 5 s on n'observe pas de réaction. De 5 à 15 s, il se produit *un dépassement poststimulatoire* dont la durée augmente avec celle de *l'intensité*. De même après 30 s de stimulation un dépassement se produit d'une manière encore plus prononcée.

COMMENTAIRES

L'analyse comparative des *réponses nystagmiques* obtenues par stimulation électrique de l'AND et par stimulation d'accélération giratoire fait ressortir un certain nombre de points communs.

La *latence au seuil* a été trouvée d'une durée de 4 à 6 secondes pour les stimulations électriques et d'une durée de 2 à 8 secondes pour les stimulations rotatoires. (Ces valeurs donnent *seulement un ordre de grandeur vu le nombre restreint d'expériences*, le calcul statistique montre qu'elles sont cependant comprises dans les limites de confiance.)

La *fréquence du nystagmus* est apparue comme le paramètre le plus intéressant et le plus facilement mesurable dans les 2 types de stimulation. *Il existe une relation significative entre l'intensité du stimulus appliqué, soit la tension électrique ou la valeur d'accélération rotatoire, et la fréquence du nystagmus*. Dans l'ensemble cette fréquence croît dans le même sens *que la valeur du stimulus, jusqu'à une valeur stable, la fréquence maxima* que l'on obtient avec le degré d'excitation choisi, en 15 à 20 secondes pour la stimulation électrique et un peu plus rapidement pour la stimulation rotatoire (environ 12 s).

Si l'on continue à appliquer le stimulus au delà d'une certaine limite de *durée* qui est de 40 à 50 secondes en stimulation électrique et de 25 à 30 *secondes en stimulation d'accélération giratoire*, au lieu de s'accroître comme on pourrait s'y attendre, la réaction semble s'épuiser. Toutefois on peut l'entretenir avec des stimulations d'une *intensité plus forte*.

D'une manière générale, on constate que l'influence de la *durée* est faible si on la compare à l'*intensité* du stimulus appliqué. La fréquence maxima du nystagmus est indépendante de la durée de l'excitation. La loi de Mulder, à laquelle on se réfère classiquement, ne conviendrait ici qu'à la période *transitoire d'installation de la réaction nystagmique*, elle ne s'applique plus à la période de *régime qui est très rapidement atteinte*.

Le *seuil* de la réaction nystagmique est plus difficile à *définir que chez l'homme*. En stimulation centrale comme en stimulation périphérique on reconnaît différents niveaux:

1) stimulation *infraliminaire* très faible sans aucune réaction quelconque.

Tension (en volts)	Latence (en secondes)	
	Animal 103	Animal 102
0,5	8	—
0,75	5 (seuil)	—
1,0	4	—
1,25	3	—
1,5	×	6 (seuil)
1,75	×	4
2,0	2	3
3,0	×	2
4,0	×	1,5
5,0	×	1

On voit que la latence décroît progressivement lorsque le niveau d'intensité du stimulus électrique augmente. Elle est ici de 4 à 6 secondes au voisinage du seuil.

Fréquence : On peut distinguer trois groupes de réponses selon la *durée d'application* du stimulus :

— courte durée (entre 5 et 15 secondes)
— durée moyenne (30 secondes) = optima
— longue durée (80 secondes ou plus)

Si l'on considère des stimulations de *durée moyenne* (30 s) et constante, on note à différents niveaux d'intensité du stimulus :

— à 0,75 V (large dispersion, étant au voisinage du seuil), la fréquence croît pendant 15 à 20 secondes, puis se stabilise à un « *plateau* » *maximum de 1,2 H*, jusqu'à l'arrêt (avec un léger dépassement de 3-4 s),
— à 1,0 V (dispersion plus petite), la fréquence croît de même assez rapidement, puis se stabilise à un maximum de *1,6 H*, avec un dépassement plus long de 6 s,
— à 1,25 V, la fréquence croît encore de même, puis se stabilise à un maximum de *1,7 H*,
— à 1,50 V, la fréquence croît toujours de même, puis se stabilise en plateau à *2,8 H*,

Il semble qu'à de plus hauts voltages, la fréquence maximum continue à augmenter jusqu'à 3,5 et 4 H_z

Pour une *stimulation de longue durée* (80 s), la fréquence atteint comme précédemment un niveau maximum, auquel elle se stabilise. Puis, selon l'intensité du stimulus deux cas peuvent se produire

1) avec une *intensité supraliminaire modérée* de 0,5 à 1,75 V, la fréquence diminue et la réaction s'épuise en 55 à 60 s,

2) avec une *forte intensité supraliminaire* (2,0 V), il n'y a pas d'épuisement

Dans une de nos expériences (à 2,0 V) nous avons même pu maintenir

das Vorhandensein einer gleichen Reaktionsschwelle, welche eine Frequenzschwelle ist,

eine schnelle Zunahme der Frequenz des Nystagmus während der ersten Periode der Stimulation,

die Einstellung einer maximalen, stabilen Frequenz, deren *Höhe (in Hz) mit* der Intensität der Stimulation zunimmt (in ° sec² oder in Volt),

die Erschöpfung der Reaktion bei einer Stimulation von langer Dauer (30 s *und mehr) und im Gegensatz* die Verlängerung der Dauer der Antwort mit dem Auftreten von nystagmischen Spätentladungen, wenn die Intensität des Stimulus elektrischer oder rotatorischer Art erhöht wird

BIBLIOGRAPHIE

LACHMANN, J., BERGMANN, F., et MONNIER, M., 1958 Central nystagmus elicited by stimulation of the mesodiencephalon in the rabbit *Amer J Physiol* 193 328

LACHMANN, J., BERGMANN, F., WEISMANN, J., et WELSER, A., 1958 Central nystagmus II Relationship between central and labyrinthine nystagmus *Amer J Physiol*, 193 267

MONNIER, M., 1943 Syndromes déviationnels provoqués par excitation et destruction du système réticulaire bulbo protubérantiel chez le chat (Manège et réaction tegmentale) *Schweiz Arch Neurol Psychiat*, 107, 84 102

MONNIER, M., et MONTANDON, P., 1961 Localisation différenciée de l'aire nystagmogène diencéphalique III° Symposium vestibulaire international Genève 1961 Confin neurol., 21 459-463

MONTANDON, A., et LEROIS, J., 1961 Effets de la suppression expérimentale de l'AND sur le nystagmus vestibulaire giratoire *Acta Oto-Laryng (Stockh)* 56 402 413

MONTANDON, P., 1964 Functional correlations between the diencephalic nystagmogenic area (DNA) and the vestibular nystagmogenic area (VNA) *Acta Oto laryng (Stockh)*, Suppl 186

NICOLAI HARTEN H., 1964 L'électronystagmogramme normal ses difficultés Thèse Marseille

Clinique O.R.L., Hôpital Cantonal
Genève Suisse

DISCUSSION

H Frey et Im Anschluss an die von Herrn Montandon gezeigten ENG Kurven, *nicht aber zu dem Inhalt* seines Vortrages zu dem ich ihn nur beglückwünschen kann *möchte ich mir* erlauben einige Bedenken bezüglich der entscheidenden *Verwertung von Elektro* Nystagmogrammen zu äussern Es sind *in letzter Zeit* ENG Befunde veröffentlicht worden deren Deutung zu äusserst aufregenden Schlussfolgerungen *geführt hat* die an den Grundlagen der Vestibularisphysiologie rütteln und bei denen gewisse Fragwürdigkeiten und Vieldeutigkeiten der Elektronystagmographie nicht immer berücksichtigt *worden zu sein scheinen* So haben Jongkees und Mitarbeiter auf der *Parallelschaukel* unter bestimmten Lage- und Blickbedingungen beim Kaninchen und beim *Menschen ENG* Kurven mit Linearbeschleunigungs Nystagmus erhalten *Die Linearbeschleunigung der* Parallelschaukel betrug nach Jongkees maximal 3 m sec² Lässt man die Linearbeschleunigung der Gravitation im Beschleunigungsfeld der Erde von g = 9 81 m sec² in beliebiger Richtung auf Mensch *oder Tier* einwirken, so entsteht aber kein Nystagmus Ein echter Linearbeschleunigungs-Nystagmus unter 9 81 m sec²

2) stimulation *infraliminaire plus forte,* produisant après une latence prolongée des secousses nystagmiques, isolées ou par groupe, d'amplitude moyenne, de type diphasique et unidirectionnel,

3) stimulation *liminaire,* donnant naissance à une périodicité caractérisant le rythme nystagmique qui est le *seuil du nystagmus,* avec une fréquence de 1 H_z (1 à 2 V ou 3°/s),

4) stimulation *supra liminaire,* caractérisée par une fréquence plus élevée et l'apparition d'un « dépassement » sur la période post-stimulatoire (post-décharge nystagmique).

Ces données expérimentales, en accord avec les précédentes obtenues dans les mêmes conditions chez le même animal, contribuent à éclairer le mécanisme de la réaction vestibulaire nystagmique au cours des épreuves rotatoires, spécialement du nystagmus perrotatoire d'accélération. Elles apportent aussi des précisions sur la valeur de certains paramètres utilisés en électro-nystagmographie clinique, tels que la durée, la fréquence ainsi que sur le seuil du nystagmus.

SUMMARY

The present experimental researches illustrate the parallelism between nystagmic responses from electrical stimulation of diencephalic centers and from rotatory stimulation of vestibular receptors. This concerns:

the *latency* which is of many seconds (4 à 6 s),

the *apparition* of a *nystagmic reaction* with regular rhythm, diphasic and horizontal jerks beating in a unique and definite direction to the right or to the left,

the *existence of the same reactional threshold* which is a frequency threshold,

a rapid increase of the nystagmic frequency during the initial period of stimulation,

the establishment of a stable maxima frequency whose level (in H_z) increases with the intensity of the stimulation (in ° sec² or in volts),

the extinction of the reaction in the long standing stimulation (80 sec and above) and inversely the increase in the duration of the response with the apparition of nystagmic post-discharges when the stimulus intensity, either electrical or rotatory, is increased.

ZUSAMMENFASSUNG

Die angeführten experimentellen Versuche lassen einen Parallelismus erkennen zwischen dem Nystagmus der durch elektrische Reizung der dienecephalen Zentren erhalten wird und dem Nystagmus der durch rotatorische Stimulation der vestibulären Rezeptoren ausgelöst wird. Dieser Parallelismus betrifft:

die *Latenzzeit*, die mehrere Sekunden beträgt,

das *Auftreten* einer *nystagmischen Reaktion* von regelmässigem Rhythmus mit diphasischen horizontalen Ausschlägen nach einer bestimmten und einzigen Richtung nach rechts oder nach links,

das Vorhandensein einer gleichen Reaktionsschwelle, welche eine Frequenzschwelle ist,

eine schnelle Zunahme der Frequenz des Nystagmus während der ersten Periode der Stimulation,

die Einstellung einer maximalen stabilen Frequenz, deren Höhe (in Hz) mit der Intensität der Stimulation zunimmt (in °/sec² oder in Volt),

die Erschöpfung der Reaktion bei einer Stimulation von langer Dauer (80 s und mehr) und im Gegensatz die Verlängerung der Dauer der Antwort mit dem Auftreten von nystagmischen Spätentladungen, wenn die Intensität des Stimulus *elektrischer oder rotatorischer* Art, erhöht wird

BIBLIOGRAPHIE

LACHMANN, J., BERGMANN, F. et MONNIER, M., 1958 Central nystagmus elicited by stimulation of the mesodiencephalon in the rabbit *Amer J Physiol* 193 328

LACHMANN, J., BERGMANN, F., WEINMANN, J. et WEINER, A., 1958 Central nystagmus II Relationship between central and labyrinthine nystagmus *Amer J Physiol* 193 267

MONNIER, M., 1943 Syndromes déviationnels provoqués par excitation et destruction du système réticulaire bulbo protubérantiel chez le chat (Manège et réaction tegmentale) *Archiv Psychiat Neurol* 107 84 102

MONNIER, M., et MONTANDON, P., 1961 Localisation différenciée de l'aire nystagmogène diencéphalique III^e Symposium vestibulaire international *Genève 1961 Confin neur* 1, 21 459 463

MONTANDON, A., et *Simons*, J., 1961 *Effets de la suppression expérimentale de l'AND sur* le nystagmus vestibulaire giratoire *Acta Oto laryng (Stockh)* 56 402–413

MONTANDON, A., 1964 Functional correlations between the diencephalic nystagmogenic area (DNA) and the vestibular nystagmogenic area (VNA) *Acta Oto laryng (Stockh)*, Suppl 186

NICCOLAI HARTER, H., 1964 L'électronystagmogramme normal ses difficultés Thèse Marseille

Clinique O.R.L. Hôpital Cantonal
Genève Suisse

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VESTIBULAR EFFERENT SYSTEM

Electrophysiological Research

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Experimental researches have been performed in order to give the *direct demonstration of* the function of the vestibular efferent system. During electric square wave stimulation at tetanic frequency of the vestibular efferent system both a reduction of the activity of the vestibular nerve and a *modification of vestibular DC resting potentials* were recorded. Stimulation with single impulses caused a discharge at the level of the contralateral vestibular nerve.

Numerous data suggest that the input from many afferent systems is controlled by centrifugal nervous pathways *and that centrifugal control* may be a general principle of action of the central nervous system. This centrifugal control may act as a "gating mechanism", suppressing sensory input of secondary importance, as a self-regulating system, where the sensory input is controlled through a feedback loop activated by the sense organ itself (Hagbarth 1960, Fex 1962, etc.).

This centrifugal control was demonstrated in the neuromuscular spindle (Granit 1955), in the bioelectrical retinal activity (Granit, 1955, Dodt, 1956, etc.), in the bioelectric activity of the olfactory bulb (Arduini & Moruzzi 1953, Kerr & Hagbarth 1955, etc.), in the cochlear function (Galambos 1956, Desmedt *et al.* 1957, 1960, 1963, Fex, 1962, Pfaltz, 1962, Antonelli 1963, etc.).

Recent histological (Petroff 1955, Wersall 1956, 1960, Engstrom, 1958, *Rasmussen & Gacek 1958, Engstrom & Wersall,* 1958, *Carpenter et al.*, 1959, Carpenter 1960, Gacek 1960) and histochemical (Dohlman *et al.* 1958, Ireland & Farkashidy 1961, Rossi & Cortesina, 1962, Hilding & Wersall 1962) researches demonstrated centrifugal efferent vestibular fibers in their terminal part at the level of the brain stem and of the vestibular receptors.

The demonstration of the physiological properties of this efferent vestibular system can be pointed out only with the aid of electrophysiological *procedure*. This demonstration was carried out by Sala (1962) and was later confirmed by Schmidt (1963), and by Gleisner & Henriksson 1964.

Experiments were undertaken with the aim of demonstrating the modifications induced by the stimulation of the efferent vestibular system (e.v.s.)

bedeutet daher geradezu eine Vestibularis-Revolution, auch wenn er nur bei verändertem Kontraktionszustand der Augenmuskeln auftritt. — Ich selbst habe bei einem doppelseitig Blinden, dessen linkes Auge nach schwerer Verletzung nur ein winziger Schrumpfbulbus war und dessen rechtes Auge enukleiert war, einen in den Stümpfen sichtbaren spontanen Vertikalnystagmus nach oben bei Ableitung am linken Auge registrieren können (Demonstration). Selbst wenn es sich nur um eine durch rhythmische Lidbewegungen vorgetäuschte Nystagmuskurve handeln sollte, (eine gleichzeitige kinematographische Kontrolle hat nicht stattgefunden), so wäre der ENG-Befund ohne Vorhandensein des normalen Dipols der Augäpfel bemerkenswert. — Das Aufregendste ist aber die neuerdings von Dittrich auf Grund von ENG-Befunden aufgestellte Behauptung, dass beim vestibulären Nystagmus nicht die langsame Phase, sondern die schnelle Phase das Primäre ist. In den soeben von Herrn Montandon gezeigten ENG-Kurven konnte man in der Tat den Beginn von Nystagmusschlägen mit einer schnellen Phase sehen. Sehr deutlich ist das auch in einem publizierten ENG des perrotatorischen Nystagmus beim Kaninchen (*Act. Otolaryng. Stockh. 56*, S. 404, Fig. 2) zu erkennen (Demonstration). Wenn man aber den Beginn eines perrotatorischen Nystagmus beim Kaninchen hinter einem Gitter f i l m t, so ist die langsame Phase zweifellos das Primäre, wie das ja aus vielfachen Tierversuchen und zahlreichen klinischen Beobachtungen bekannt ist (Projektion einer Filmschleife ohne Ende, die in beliebig häufiger Wiederholung jeweils den Beginn des perrotatorischen Nystagmus zeigt). Es ist physiologisch ganz unwahrscheinlich, dass es verschiedene Möglichkeiten des Nystagmusbeginns gibt, wenn zusätzliche nicht vestibuläre Faktoren wie z. B. bei den *aktiven* Kopfdrehungen des Menschen vermieden werden. Man sollte daher, wenn grundsätzlich wichtige Fragen der Vestibularisphysiologie auf Grund von ENG-Befunden beantwortet werden sollen, die *Gitter-Kinematographie* zur Kontrolle heranziehen. — Übrigens hat bereits Groen, wie ich erst nachträglich durch einen Hinweis Huizingas erfuhr, beim französischen Kongress in Paris 1963 betont, dass die langsame Phase die primäre Phase ist und zum Ausdruck gebracht, dass «cette théorie de Dittrich provient d'une petite faiblesse de son instrument électronique» (*Comptes rendues des Séances 1963*, Librairie Arnette, Paris 1964, S. 230).

A. *Montandon* (Réponse): Je pense que le Professeur *Frenzel*, dont nous apprécions l'utile contribution à l'étude du nystagmus au moyen des lunettes spéciales qu'il a imaginées et dont nous servons toujours, ne saurait mettre en doute la valeur de l'ENG, qui permet l'enregistrement graphique d'une telle réaction vestibulaire. Celle-ci constitue en effet l'un des paramètres essentiels de l'examen clinique des canaux semi-circulaires. Le nystagmus qu'il a enregistré chez un animal privé de ses globes oculaires est sans doute (du point de vue oculaire!) un artefact.

Quant au film et à la question de la phase initiale, je pense que dans le cas démontré il s'agit effectivement de la phase lente. Je ne crois pas toutefois qu'il soit absolument certain que *dans tous les cas* ce phénomène soit initial et je pense que le problème mérite encore d'être examiné sous ses différents aspects.

Second procedure

Tetanic electric stimulation of the e v s was performed and action potentials of the contralateral vestibular nerve were recorded (*Fig 1*)

Results During this stimulation spontaneous action potentials of the contralateral vestibular nerve underwent a distinct reduction in frequency

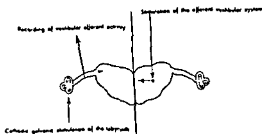


Fig 2 Third procedure

Third procedure

Tetanic electric stimulation of the e v s was carried out during the cathodic galvanic polarisation of the contralateral labyrinth (Fig 2)

Results Tetanic stimulation reduces the *frequency of the potentials* induced by cathodic polarisation of the labyrinth

(B) *Efferent Influence on Vestibular DC Resting Potentials*

The second series of the experiments was performed by recording vestibular DC resting potentials surrounding the membranous labyrinth

Ledoux (1958) and Dohlman (1960) emphasized the importance of these DC labyrinthine resting potentials as generator potentials of the vestibular nerve afferent activity Trincker (1959) observed that the cupula utriculopetal deflection causes a depolarisation of the crista of the horizontal ampulla while the cupula utriculofugal deflection causes a hyperpolarisation Trincker (1953) and Eldredge *et al* (1961) calculate the absolute values of the labyrinthine DC resting potentials at the level of the membranous labyrinth (walls crista ampulla etc)

This is important to outline that we aimed at recording not the absolute values of the vestibular DC resting potentials but *only their modifications* during the stimulation of the efferent vestibular system

The vestibular DC resting potentials were recorded by us in decerebrated cat The tip of the thin chlorided silver wire was placed in a drillhole bored by microdrill at the level of the crus commune The indifferent electrode was placed upon the skull bone The electrodes were connected with a highly sensitive microvoltmeter Hewlett Packard The diameter of the electrodes was 0 15 mm at the tip

The use of metallic electrodes in the recording of the vestibular DC resting potentials (vest DC r p) is known to cause artifacts due to contact

in the afferent vestibular activity. The afferent activity was recorded at the level of the vestibular nerve (first series of experiments) as well as at the level of the vestibular receptors (second series of experiments). Thus it was possible to study what the effect of the vestibular efferent system is both on (*a*) the action potentials of the vestibular nerve, and (*b*) on the DC resting potentials of the vestibular receptors themselves.

(A) *Efferent Influence on Vestibular Nerve Activity*

Action potentials of the vestibular nerve were recorded upon the intact vestibular nerve, after suction of the cerebellum, by a steel microelectrode with a diameter of 30–40 microns at the tip, connected with an AC preamplifier Tektronik and cathode ray oscilloscope.

To be sure that the recording electrode was placed exactly on the vestibular nerve, galvanic stimulation using the Loewenstein (1955) technique was performed. Cathodic polarisation of the labyrinth caused an increase of nerve action potentials, whereas anodic polarisation provoked their disappearance.

Electric square wave stimulation of the floor of the IV ventricle was performed in the contralateral vestibular area (Deiters' nucleus region) by means of bipolar electrodes mounted on a micromanipulator fixed to the Horsley-Clarke apparatus. The parameters of the stimulation were: single and repetitive impulses, 4–6 V of intensity, 0.5 msec of duration of single impulse.

First procedure

Electric stimulation of the e.v.s. was performed with *single* impulses, and action potentials of the contralateral vestibular nerve were recorded (Fig. 1).

Results. This stimulation elicited a discharge at the level of the vestibular nerve (monophasic positive and negative spikes, diphasic spikes). Repeated stimulation with single impulses shows burst in unit of the vestibular nerve. The latency was between 22–32 msec.

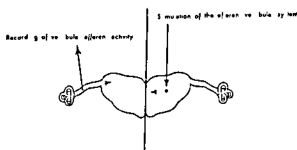


Fig. 1. First and second procedures.

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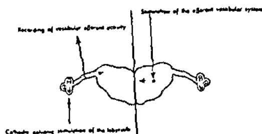


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This is important to outline that we aimed at recording not the absolute values of the vestibular DC resting potentials but only their modifications during the stimulation of the efferent vestibular system

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The use of metallic electrodes in the recording of the vestibular DC resting potentials (vest DC r p) is known to cause artifacts due to contact

potentials (Eldredge *et al.*, 1961). To overcome this obstacle we used Schmidt & Fernandez's (1962) technique: the tip of the active electrode was placed on the bone near the small niche bored into the petrous bone and the microvoltmeter was adjusted to zero. The electrode was then shifted into the niche. Following this step we constantly observed the appearance of a positive potential which was to be ascribed to the vest. DC r p against the petrous bone.

The microvoltmeter was then connected with the first canal of the cathode ray oscilloscope ETC model h 121 A.

Thermic stimulation of the labyrinth was performed with warm water (30 cc of water at 50°C injected within 30″) and cold water (30 cc of water at 5°C injected within 30″). When the thermic irrigation did not cause any evident nystagmus this criterion was used as a basis for elimination

In this second series of experiments, electronic square wave stimulation was performed by means of two microelectrodes, thinned down to 30 microns by means of electrolysis and insulated except at the tip The interelectrode distance at the tips was 0 5 mm. The parameters of the stimuli were. optimal frequency between 150–300 impulse/sec (tetanic burst), duration of single impulse: 0 5 msec; strength expressed in voltage output of the stimulator. 2–6 V.

Stimulation of the e.v.s. was carried out at various parts of the contralateral and ipsilateral areas of the two Deiters' nuclei, and at the level of the raphe between the two Deiters' nuclei The specificity of these stimulated points (localized by stereotaxis coordinates, and by electrolytic coagulation and histological control) was demonstrated by the fact that the least shifting of the stimulating electrodes causes the disappearance of the phenomena resulting from the stimulation of the e v s Square wave stimuli were directly recorded in the second canal of the cathode ray oscilloscope, since stimulation did not provoke artifacts of the trace of the vest DC r p

Fourth procedure

Thermic stimulation of one labyrinth was carried out (warm and cold water) and vest DC r p of both labyrinths were recorded simultaneously (Fig 3)

Results Thermic stimulation caused a constant variation in the vest DC r p of this labyrinth In particular, the warm thermic stimulation causes a depolarisation of the vest DC r p (according to Trincker, 1959, etc.) and the cold one a hyperpolarisation The change in the vest DC r p was maximally of 300 microvolts The thermic stimulation evoked an ocular nystagmus with the fast component directed ipsilaterally after warm thermic stimulation and contralaterally after cold thermic stimulation The jerks struck in the transversal plane of the orbit

Thermic stimulation of one labyrinth causes the *contemporaneous* appearance of opposite phenomena at the level of the *contralateral labyrinth*, that is, warm thermic stimulation causes hyperpolarisation, the cold one

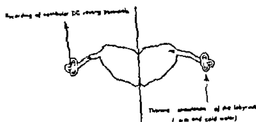


Fig 3 Fourth procedure

depolarisation *The intensity* of these variations of the vest DC r p in the contralateral labyrinth is maximally of 150 microvolts and the duration is generally shorter (Table 1)

Table 1 *Feedback loop between the two labyrinths*

Right labyrinth	Left labyrinth
Warm water → Depolarisation Cold water → Hyperpolarisation	→ Hyperpolarisation → Depolarisation

Warm water irrigation of one ear causes a depolarisation of the DC resting potentials of the ipsilateral labyrinth and simultaneously a hyperpolarisation of DC resting potentials of the contralateral labyrinth

Cold water irrigation of one ear causes a hyperpolarisation of the DC resting potentials of the ipsilateral labyrinth and simultaneously a depolarisation of DC resting potentials of the contralateral labyrinth

The modifications of DC resting potentials of the nonstimulated labyrinth appear after a longer latency and reach a smaller intensity

Fifth procedure

The electric stimulation of the c v s (contralateral and ipsilateral areas of Deiters nuclei, and at the level of the raphe between the two Deiters' nuclei) was performed (Fig 4) The vest DC r p of both labyrinths were recorded The electric stimulus lasted for a long period (over 150–200 msec)

Results The modifications induced in the vest DC r p behave differently

The increase of the vest D C r p, once the maximal intensity was reached, would begin to decrease slowly though the stimulation lasted At interruption of stimulation the r p returned to their original values and a slight fall of the r p under the prestimulatory level was observed

In other preparations, the increase of vest DC r p remained unchanged throughout the duration of the stimulus and no fall under the prestimulatory level appeared at interruption of stimulation

The latency between stimulation of the c v s and the beginning of the increase of vest DC r p was between 9–12 msec These effects had a slightly smaller intensity when the ipsilateral region of Deiters' nucleus was stimulated

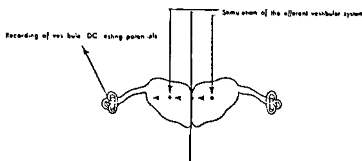


FIG. 4. Fifth and sixth procedures

Sixth procedure

Tetanic burst of the e.v.s. was extremely short (20 msec) and occurred several times at regular intervals of about 150 msec, for one minute (Fig. 4).

Results. Every impulse was followed by a clear short hyperpolarisation of the vest. DC r.p., which disappeared quickly as the stimulus stopped, and was followed by a shorter and slighter depolarisation; this depolarisation stopped after 50 sec of repetitive stimulation.

Seventh procedure

Strychnine sulphate was administered intravenously (0.10 mg/body kg) in order to study its effect during stimulation of the e.v.s., following the technique used by Desmedt *et al.* (1957, 1960, 1963) and Fex (1962), in their experiments on the cochlear efferent system. It is known that these AA. by this way blocked the effect of electrical stimulation of Rasmussen's bundle on cochlear potentials.

Results. The intravenous administration of strychnine sulphate in subconvulsant doses caused the abolition of the modifications induced on the vest. DC r.p. by the stimulation of the e.v.s.

Eighth procedure

The electric stimulation of the e.v.s. was performed as soon as the thermic stimulation had reached the maximal modifications of the vest. DC r.p. (Fig. 5).

Results. The electric stimulation produced a hyperpolarisation of the DC r.p. which increased the hyperpolarisation caused by cold water stimulation and reduced the depolarisation induced by warm water stimulation.

Further I should like to remark that the long latency between the stimulation of the floor of the IV ventricle and the appearance of the potentials of the contralateral nerve (and of the modifications of vest. DC r.p.) allows us to exclude an antidromic conduction of the stimuli. If there were an antidromic discharge the two phenomena would be almost superimposed. Besides, primary vestibular afferent fibers do not cross the midline (Walberg *et al.* 1958). Furthermore, a midline shallow cut of the floor of the IV

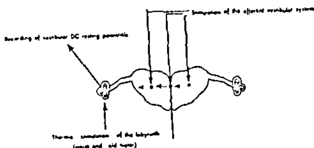


Fig. 5. Eighth procedure

ventricle causes the disappearance of the above phenomena, if it were a matter of an aspecific diffusion of the stimulus through the nervous tissue, the stimulus would be conducted over the midline section. And, moreover, the least shifting of the stimulating electrodes in the brain stem is sufficient to make these phenomena disappear.

These results supported the validity of Granit's supposition, that is, that the afferent messages from relatively slow adapting receptors are under the central nervous system control, particularly the reticular substance of the brain stem, which can modulate their activity through efferent nerve fibers arriving at the level of the receptors themselves, and furthermore we may consider under a new light some common observations in human pathology because the demonstration of the physiological properties of the e. v. s. constitutes a subject which enters into the modern concept of psychosomatic medicine.

RÉSUMÉ

Des recherches expérimentales ont été conduites pour donner la démonstration de l'activité du système vestibulaire efférent. La stimulation électrique de ce système a donné une modification de l'activité bioélectrique du nerf vestibulaire controlatérale et des potentiels vestibulaires continus de repos.

ZUSAMMENFASSUNG

Es wurden experimentelle Untersuchungen durchgeführt, um eine direkte Veranschaulichung der Funktion des efferenten Vestibularsystems zu geben. Während der Reizung des efferenten Vestibularsystems ist in Höhe der Vestibularnerven eine Reduktion der spontanen Aktivität und eine Veränderung der Bestandspotentiale der vestibularen Rezeptoren registriert worden. Es wurde auch eine bioelektrische Tätigkeit des Vestibularnerven der Gegenseite bewiesen.

REFERENCES

Antonelli, A. R., 1963. Modificazione della trasmissione talamo—corticale degli impulsi uditivi per effetto di meccanismi centrali. *Minerva Otorinolaring.*, 13: 302.

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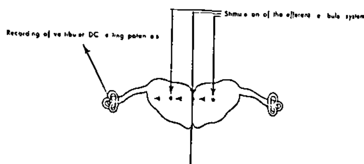


FIG 4 Fifth and sixth procedures

Sixth procedure

Tetanic burst of the e v s was extremely short (20 msec) and occurred several times at regular intervals of about 150 msec, for one minute (Fig 4)

Results Every impulse was followed by a clear short hyperpolarisation of the vest DC r p, which disappeared quickly as the stimulus stopped, and was followed by a shorter and slighter depolarisation, this depolarisation stopped after 50 sec of repetitive stimulation

Seventh procedure

Strychnine sulphate was administered intravenously (0 10 mg/body kg) in order to study its effect during stimulation of the e v s, following the technique used by Desmedt *et al* (1957, 1960, 1963) and Fex (1962), in their experiments on the cochlear efferent system It is known that these AA by this way blocked the effect of electrical stimulation of Rasmussen's bundle on cochlear potentials

Results The intravenous administration of strychnine sulphate in sub convulsant doses caused the abolition of the modifications induced on the vest DC r p by the stimulation of the e v s

Eighth procedure

The electric stimulation of the e v s was performed as soon as the thermic stimulation had reached the maximal modifications of the vest DC r p (Fig 5)

Results The electric stimulation produced a hyperpolarisation of the DC r p which increased the hyperpolarisation caused by cold water stimulation and reduced the depolarisation induced by warm water stimulation

Further I should like to remark that the long latency between the stimulation of the floor of the IV ventricle and the appearance of the potentials of the contralateral nerve (and of the modifications of vest DC r p) allows us to exclude an antidromic conduction of the stimuli If there were an antidromic discharge the two phenomena would be almost superimposed Besides, primary vestibular afferent fibers do not cross the midline (Walberg *et al*, 1958) Furthermore, a midline shallow cut of the floor of the IV

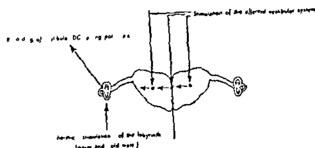


FIG 5 Eighth procedure

ventricle causes the disappearance of the above phenomena, if it were a matter of an aspecific diffusion of the stimulus through the nervous tissue, the stimulus would be conducted over the midline section And, moreover, the least shifting of the stimulating electrodes in the brain stem is sufficent to make these phenomena disappear

central nervous system control, particularly the reticular substance of the brain stem, which can modulate their activity through efferent nerve fibers arriving at the level of the receptors themselves, and furthermore we may consider under a new light some common observations in human pathology because the demonstration of the physiological properties of the e v s constitutes a subject which enters into the modern concept of psychosomatic medicine

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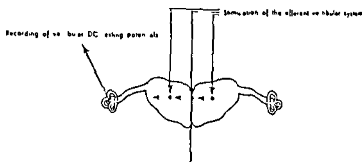


FIG. 4. Fifth and sixth procedures.

Sixth procedure

Tetanic burst of the e.v.s. was extremely short (20 msec) and occurred several times at regular intervals of about 150 msec, for one minute (Fig. 4).

Results. Every impulse was followed by a clear short hyperpolarisation of the vest. DC r.p., which disappeared quickly as the stimulus stopped, and was followed by a shorter and slighter depolarisation; this depolarisation stopped after 50 sec of repetitive stimulation.

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Results. The intravenous administration of strychnine sulphate in subconvulsant doses caused the abolition of the modifications induced on the vest. DC r.p. by the stimulation of the e.v.s.

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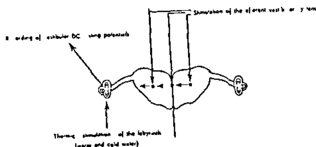


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These results supported the validity of Granit's supposition, that is, that the afferent messages from relatively slow adapting receptors *are under the* central nervous system control, particularly the reticular substance of the *brain stem, which can modulate their activity* through efferent nerve fibers arriving at the level of the receptors themselves and furthermore we may consider under a new light some common observations in human pathology because the demonstration of the physiological properties of the e v s constitutes a subject which enters into the modern concept of psychosomatic medicine

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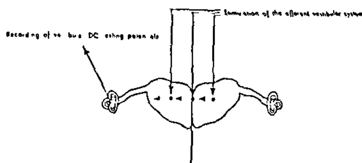


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Results. Every impulse was followed by a clear short hyperpolarisation of the vest DC r p , which disappeared quickly as the stimulus stopped, and was followed by a shorter and slighter depolarisation; this depolarisation stopped after 30 sec of repetitive stimulation.

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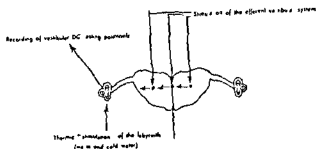


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REFERENCES

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Arduini A., and Moruzzi, G., 1953 *a* Sensory and thalamic synchronisation in the olfactory bulb *EEG Clin Neurophysiol*, *5*, 234

— 1953b Olfactory arousal reactions on the "cerveau isolé" in cat *EEG Clin Neurophysiol* 5, 243

BRODAL, A., POMPEIANO O., and WALBERG F., 1962 *The Vestibular Nuclei and their Connections Anatomy and Functional Correlations* Olives & Boyd Edinburgh and London

CARPENTER, M B 1960 Experimental anatomical physiological studies of the vestibular nerve and cerebellar connections In *Neural Mechanisms of the Auditory and Vestibular Systems* Ch C Thomas Springfield (Ill), p 297

CARPENTER M B BARD D S, and ALLING F A 1959 Anatomical connections between the fastigial nuclei, the labyrinth and the vestibular nuclei in the cat *J Comp Neurol*, *III* I

DESMEDT, J E 1960 Neurophysiological mechanisms controlling acoustic input In *Neural Mechanisms of the Auditory and Vestibular Systems* Ch C Thomas Springfield (Ill), p 152

DESMEDT, J E, and MECHELSE, K 1957 Sur un phenomene d inhibition centrifuge dans la voie acoustique centrale chez le chat *C R Soc Biol* (Par) *151* 2200

DESMEDT, J E, and LA GRUTTA, V 1963 Function of the uncrossed efferent olivo cochlear fibers in the cat *Nature 200* 472

DODT E 1956 Centrifugal impulses in rabbit's retina *J Neurophysiol 19* 301

DOHLMAN G., 1960 Some aspects of the mechanisms of vestibular haircell stimulation *Confin Neurol 20* 169

DOHLMAN, G FARKASHIDY, J, and SALONNA F 1958 Centrifugal nerve fibers to the sensory epithelium of the vestibular labyrinth *J Laryng 72* 984

ELDREDGE D H SMITH C A, DAVIS, H and GANNON, R P, 1961 The electrical polarisation of the semicircular canals (guinea pig) *Ann Otol 70* 1024

ENGSTROM H 1958 On the double innervation of the sensory epithelia of the inner ear *Acta Otolaryng* (*Stockh*), *49* 109

ENGSTROM H., and WERSALL, J, 1958 The ultrastructural organization of the organ of Corti and the vestibular sensory epithelia *Exp Cell Res* Suppl 5 460

FEX J 1962 Auditory activity in centrifugal and centripetal cochlear fibers in cat (a study of a feedback system) *Acta Physiol Scand 58* Suppl *189*

GACEK R R 1960 Efferent component of the vestibular nerve In *Neural Mechanisms of the Auditory and Vestibular Systems* Ch C Thomas Springfield (Ill) p 276

GALAMBOS R 1956 Suppression of the auditory nerve activity by stimulation of efferent fibers to the cochlea *J Neurophysiol 19* 424

GLEISNER L and HENRIKSSON N G 1964 Efferent and afferent activity pattern in the vestibular nerve of the frog *Acta Otolaryng* (*Stockh*) *58* Suppl *192* 90

GRANIT R 1955 *Receptors and Sensory Perception* Yale Univ Press

GRANIT R POMPEIANO O and WALTMAN B 1959 The early discharge of mammalian muscle spindles at onset of contraction *J Physiol 147* 399

HAGBARTH K E 1960 Centrifugal mechanisms of sensory control *Ergebn Biol 22* 47

HILDING D and WERSALL J 1962 Cholinesterase and its relations to the nerve endings in the inner ear *Acta Otolaryng* (*Stockh*) *55* 205

IRELAND P E and FARKASHIDY J 1961 Studies on the efferent innervation of the vestibular end organs *Ann Otol 70* 490

KERR D I B and HAGBARTH K E 1955 An investigation of olfactory centrifugal fiber system *J Neurophysiol 18* 362

LEDOUX A 1958 Les canaux semicirculaires *Acta Med Belg* Bruxelles

LOEWENSTEIN O 1955 The effect of galvanic polarisation on the impulse discharge from sense endings in the isolated labyrinth of the Thornback Ray (raia clavata) *J Physiol 127* 104

PETROFF, A L 1955 An experimental investigation of the origin of efferent fiber projections to the vestibular neuroepithelium *Anat Rec 121* 352

PFALTZ, R., 1962. Centrifugal inhibition of afferent secondary neurons in the cochlear nucleus by sound. *J. Acoust. Soc. Amer. 34*, 1472.
RASMUSSEN, G. L., 1942. An efferent cochlear bundle. *Anat. Rec. 82*, 441.
RASMUSSEN, G. L., and GACEK, R. R., 1958. Concerning the question of the efferent fiber component of the vestibular nerve of the cat. *Anat. Rec. 130*, 361.
ROSSI, G. and CORTESINA, G., 1962. Il sistema efferente colinergico cocleo-vestibulare. *Minerva Otorinolaring. 12*, 173.
SALA, O., 1962. Modificazioni dell' attività del nervo vestibolare a seguito della stimolazione del sistema vestibolare efferente. *Boll. Soc. Ital. Biol. Sper. 38*, 1048.
— 1963. Modifications of the vestibular nerve activity by stimulation of the efferent vestibular system. *Experientia 19*, 39.
— 1963. Effetti della stimolazione ad alta frequenza del sistema vestibulare efferente. *Boll. Soc. Ital. Biol. Sper., 39*, 872.
— 1963. Ricerche elettrofisiologiche sul sistema vestibolare efferente. *Il Valsalva 39*, 9.
— 1964. Modificazioni dei potenziali continui labirintici a seguito della stimolazione del sistema vestibolare efferente. *Boll. Soc. Ital. Biol. Sper. 40* (in press).
— 1964. The efferent vestibular system. *Acta Otolaryng. (Stockh.)* Suppl. *197*.
SCHMIDT, R. S., 1963. Frog labyrinthine efferent impulses. *Acta Otolaryng. (Stockh.) 56*, 51.
SCHMIDT, R. S., and FERNANDEZ, C., 1962. Labyrinthine DC potentials in representative vertebrates. *J. Cell. Comp. Physiol. 59*, 311.
TRINCKER, D., 1959. Electrophysiological studies of the labyrinth of the guinea pig. I. II. III. by Trincker and Partsch. *C. J. Ann. Ot. I. 68*, 145.
WALBERG, F., BOWSHER, D., and BRODAL, A., 1958. The termination of primary vestibular fibers in the vestibular nuclei in the cat. An experimental study with silver methods. *J. Comp. Neurol. 110*, 391.
WERSÄLL, J., 1956. Studies on the structure and innervation of the sensory epithelium of the cristae ampullares in the guinea pig. *Acta Otolaryng. (Stockh.)* Suppl. *126*, 1.
— 1960. Electron micrographic studies of vestibular hair cell innervation. In *Neural Mechanisms of Auditory and Vestibular Systems*. Ch. C. Thomas, Springfield (Ill.), p. 247.

Dept. of Otolaryngology, University of Padua, Italy

DISCUSSION

W. D. Keidel: What kind of electrodes did you use for recording the DC potentials and where was the location of the reference electrode?

O. Sala (Reply): I thank Prof. *Keidel* very much for his kindness. In the first series of my experiments I used steel microelectrodes (30 microns at the tip). In the second series I used two chlorided silver wires (0.15 mm at the tip) connected with a microvoltmeter Hewlett Packard. The tip of the reference electrode was placed in a drillhole bored by microdrill at the level of the crus commune.

MODIFICATIONS OF THE ACTIVITY OF THE VESTIBULAR NUCLEI IN THE CAT, FOLLOWING STIMULATION OF THE TEMPORAL LOBE

M. ARSLAN and G. A. MOLINARI
Padua, Italy

From the Ear, Nose and Throat Department (Head: Prof. M. Arslan), University of Padua

Experimental investigations in the cat have demonstrated the following modifications of the activity of the vestibular nuclei: (a) galvanic stimulation of the receptors causes either increase or reduction or no change of activity in deitersian units, (b) stimulation of the temporal area causes changes of frequency and rhythm in ipsilateral and sometimes in contralateral deitersian units.

Clinical observations and experimental researches have amply demonstrated that the activity of the vestibular apparatus is regulated by impulses from the cerebral cortex and the subcortical centres. In fact, the lesion or stimulation of these centres both in the animal and in man, determine particular modifications of the vestibular reflexes, above all the vestibular-ocular reflex (Fitzgerald & Hallpike, 1942, Carmichel *et al.*, 1954, Arslan, 1949, Hakas & Kornhuber, 1959, Wyers & Spiegel, 1953, Silverstein, 1962, Rigotti & Sala, 1948, etc.)

It is still discussed to-day at what point of the ocular vestibular reflex arc the inhibiting and coordinating action of the supravestibular structures takes place. It is, in fact, well known that the arc of the nystagmic reflex is made up of receptors and vestibular nerves, vestibular nuclei and the reticular substance strictly correlated with them, ocular motoneurons.

The importance of the reticular substance, as a structure of mediation and integration of the reflex and automatic motory activity has been demonstrated by numerous researches (Magoun, 1953, Moruzzi, 1956, Granit, 1955, etc.) The results obtained by these authors make it possible to affirm that the reticular substance undoubtedly makes up an obligatory mediation zone between vestibular reflexes and the coordinating activity of the higher nervous structures.

One cannot, however, exclude that the cortical and subcortical centres carry out their control on the ocular-vestibular reflex also at the level of the ocular motoneurons. In fact, between the cortex and the ocular-motor nuclei exist direct and very definite anatomical pathways, and the research works carried out by Di Giorgio (1940), Manni & Menzio (1952), Menzio (1952), Kluzer & Hahn (1954) have demonstrated the influence

of these connections on the nystagmic reflex It is, moreover, a common clinical observation that when there is a serious disorder or absence of the ocular motory reflex impulses (serious myopia, blindness) there is also vestibular hyperreflexia, even of a severe degree, without it being possible to demonstrate any anatomo functional alteration of the vestibular apparatus

On the contrary, it is not yet quite clear if the control of the higher encephalic centres on the ocular vestibular reflex carries also on the vestibular nuclei

The vestibular nuclei are amply represented at the level of the brain stem (see nuclei f, x, z recently demonstrated by Brodal et al, 1962) Given the close anatomical physiological relations between the reticular substance of the brain stem and the vestibular nuclei (Gernandt & Thulin, 1953, Rossi & Zanchetti 1957, etc), and given the fact that the ocular vestibular reflex operates at the level of this structure (Lorente de No, 1938), are we to consider the vestibular nuclei only as relays for labyrinthine impulses or, on the contrary as having a particular functional dignity besides their anatomical value? The problem we have set ourselves is truly complex and a series of experimental researches are required in order to attain a sound conclusion

This series of researches was meant to find out if like to what had been demonstrated for the ocular motoneurons and the reticular substance of the brain stem, a direct action of the supernuclear structures on the vestibular nuclei themselves could be demonstrated even if mediated through a polysynaptic system actually, anatomical researches could demonstrate no direct cortico vestibular pathways

RESEARCH TECHNIQUE

The research was carried out on adult cats Under ether anaesthesia the animals were tracheotomized, a pipe was inserted and artificial respiration was practised on them after the administration of d tubocurarina parenterally The animal was then placed in Horseley Clarke stereotactic apparatus, where the opening of the medial and posterior cranial fossa was undertaken

With the help of the stereotactic coordinates, a monopolar electrode (a steel wire electrolytically thinned down to a diameter inferior to 20 microns and completely isolated except at the tip) was fixed into Deiters' nucleus The electric activity of the single neurons was registered by a cathodic ray oscillograph previously amplified by a preamplifier with resistance capacity

The stimulation of the cortical areas was carried out by placing on the surface the positive pole of a galvanic circuit, in which the intensity of the current could be manually varied from O-IO mA The stimulating electrode was a little cottonwool soaked in physiological solution The same method

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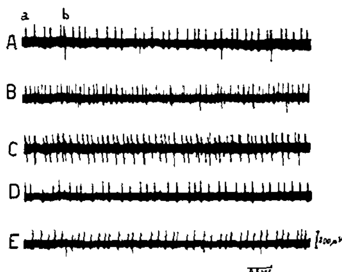


FIG. 1 Different effects excited upon two units of the nucleus of Deiters by stimulation of the labyrinth and temporal cortex

Curarized cat (A) Spontaneous activity of two units (*a* and *b*) in the right nucleus of Deiters recorded simultaneously and discharging at different speeds. (B) Cathodal polarization of the ipsilateral labyrinth with 0 2 mA increases only the frequency of discharge of the unit *a* (C) Anodal polarization of the right temporal cortex with 0 2 mA produces an increase in the frequency of discharge both of the units *a* and *b* (D) Immediately after the end of the stimulation the spontaneous activity of the unit *a* returns and the unit *b* is inhibited (E) Control at two minutes after the stimulation

was employed to stimulate the labyrinth, by introducing the electrodes into the animal's bullae that had previously been opened through the submandible

RESULTS

Our experiments have further demonstrated that Deiters' nucleus presents spontaneous electrical activity (Figs 1 A and 2 A), as Adrian (1943), Gernandt (1950), etc have already observed This activity, as De Vito *et al.* (1956) have pointed out, can be modified by galvanic stimulation of the labyrinth in particular the cathodic stimulation of the homolateral labyrinth as regards the vestibular nucleus under examination determines an increase of the dischage frequency of nearly all the active units, while the anodic stimulation determines even complete inhibition This phenomenon, characteristic of the neurons belonging functionally to the vestibular nuclei, allowed us during the experiment to control if the electrode had been placed in Deiters' nucleus (Fig 1 B)

The galvanic stimulation, positive surface, of the temporal lobe, homolateral to the vestibular nucleus from which was recorded the activity has determined some phenomena

The greater part of the vestibular neurons examined underwent an increase of the dischage frequency that lasted for the whole stimulation time

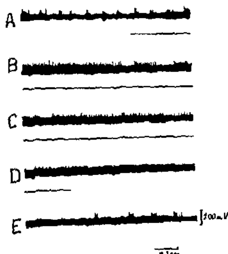


FIG 2 Effects of stimulation of the temporal cortex upon *spontaneous discharge* of units of the ipsilateral nucleus of Deiters

Curarized cat The black line indicates anodal polarization of the temporal cortex (0 2 mA) (A) Spontaneous activity of one unit of the right nucleus of Deiters. (*B & C*) Anodal polarization of the ipsilateral temporal cortex increases the *frequency* of the unit (D) Immediately after the end of the stimulation the *spontaneous activity* of the unit is inhibited (E) After some seconds the frequency of *discharge of the unit* returns to previous values

(Figs 1 C 2 B C) When the stimulus was removed, some units returned to the initial frequency at once, others only after a *short and* variable period of inhibition (Figs 1 D, 2 D)

Some examined vestibular neurons were inhibited by *the cortical* stimulation and took up their primitive activity of *discharge again* when the stimulation ceased either immediately or after a short rebound period in which the frequency was greater than the initial frequency

Some units of Deiters nucleus that *responded to* the cortical stimulation were not influenced *by the labyrinthine* stimulation (Fig 1)

The decerebration of the animal *carried out* with the precollicolar section of the brain stem leaving the *brain in situ* determined the disappearance of every *effect of the* cortical *polarization on* the activity of the vestibular neurons this allowed us to *exclude that* these phenomena were due to the diffusion of the *electric stimulus* through the cerebral *substance*

DISCUSSION AND CONCLUSIONS

The results of our experiments have *for* the first time presented the demonstration that the activity of the vestibular nuclei can be modified by stimulation of the temporal *cortical* areas This function of *cortical* control

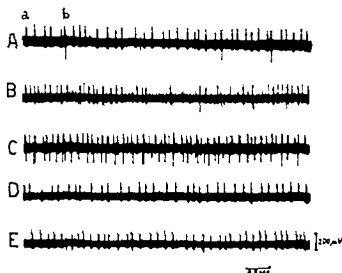


Fig. 1. Different effects exerted upon two units of the nucleus of Deiters by stimulation of the labyrinth and temporal cortex.

Curarized cat. (A) Spontaneous activity of two units (*a* and *b*) in the right nucleus of Deiters recorded simultaneously and discharging at different speeds. (B) Cathodal polarization of the ipsilateral labyrinth with 0.2 mA increases only the frequency of discharge of the unit *a*. (C) Anodal polarization of the right temporal cortex with 0.2 mA produces an increase in the frequency of discharge both of the units *a* and *b*. (D) Immediately after the end of the stimulation the spontaneous activity of the unit *a* returns and the unit *b* is inhibited. (E) Control at two minutes after the stimulation.

was employed to stimulate the labyrinth, by introducing the electrodes into the animal's bullae that had previously been opened through the submandible.

RESULTS

Our experiments have further demonstrated that Deiters' nucleus presents spontaneous electrical activity (Figs. 1 A and 2 A), as Adrian (1943), Gernandt (1950), etc. have already observed. This activity, as De Vito *et al.* (1956) have pointed out, can be modified by galvanic stimulation of the labyrinth: in particular the cathodic stimulation of the homolateral labyrinth as regards the vestibular nucleus under examination determines an increase of the discharge frequency of nearly all the active units, while the anodic stimulation determines even complete inhibition. This phenomenon, characteristic of the neurons belonging functionally to the vestibular nuclei, allowed us during the experiment to control if the electrode had been placed in Deiters' nucleus (Fig. 1 B).

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Brodal, A., Pompeiano, O., and Walberg, F., 1962 *The Vestibular Nuclei and their Connections Anatomy and Functional Correlation* Oliver & Boyd Edinburgh and London
Carmichael, E. A., Dix, M. R., and Hallpike, C. S., 1954 Lesions of the cerebral hemispheres and their effect upon optokinetic and caloric nystagmus *Brain* 77 345
de Vito, R. V., Brusa, A., and Arduini, A., 1956 Cerebellar and vestibular influences on deitersian units *J Neurophysiol* 19 241
di Giorgio, A. M., 1940 Fisiologia dei centri vestibolari *Tratt Ital di Pat ORL* Ed Zanichello Bologna
Fitzgerald, G., and Hallpike, C. S., 1942 Studies in human vestibular function 1 Observations on the directional preponderance of caloric nystagmus resulting from cerebral lesions *Brain* 65 115
Gernandt, B. E., 1950 Midbrain activity in response to vestibular stimulation *Acta Physiol Scand* 21 73
Gernandt, B. E., and Thulin, C. A., 1955 Reciprocal effects upon spinal motoneurons from stimulation of bulbar formation *J Neurophysiol* 18 113
Granit, R., 1955 *Receptors and Sensory Perception* New Haven Yale University Press
Hakas, P., and Kornhuber, H. H., 1953 Der vestibulare Nystagmus bei Grosshirnlasionen des Menschen *Arch Psychiatr Nervenkr* 27 19
Kreizer, G., and Hahn, R., 1954 Considerations sur la prédominance unilaterale du nystagmus vestibulaire provoque chez des sujets atteints de tumeur d un hémisphere cerebral *Rev Otoneuroophthalm* 26 257
Lorente de Nó, R., 1938 Analysis of the activity of the chains of internuncial neurons *J Neurophysiol* 1 207
Magoun, H. W., 1953 Physiological interrelationship between cortex and subcortical structures *EEG Clin Neurophysiol* Suppl 4 163
Mancini, I., and Menzio, P., 1952 Effetti di lesioni della meninge sulle reazioni oculari vestibolari *Arch Ital Otol* 63 491
Menzio, P., 1952 Modificazione della reflettivita labirintica nell uomo da alterazioni meningee *Arch Ital Otol* 63 529
Moruzzi, G., 1956 Spontaneous and evoked electrical activity in the brainstem reticular formation *Abstr Rev XX Int Physiol Congr Bruxelles* p 269
Rizzotti, S., and Sala, O., 1948 Ricerche sul comportamento delle reazioni vestibolari nel coniglio dopo asportazione del telencefalo *Acta Neurologica* 3 1
Rossi, G. F., and Zanchetti, A., 1957 The brainstem reticular formation *Arch Ital Biol* 95 199
Silverstein, H., 1962 The cortical influence on the vestibular apparatus *AMA Arch Otolaryng* 6 158
Wacis, H. T., and Spiegel, E. A., 1953 Effect of cortical lesions and elimination of retinal impulses of labyrinthine nystagmus *AMA Arch Otolaryng* 57 1

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DISCUSSION

W. D. Keidel In one slide of your fine presentation you showed an effect of stimulation where after the onset of the stimulus a large overshoot in the increase of the numbers of spikes per second was followed by a considerable drop even beneath the zero line Then after a silent period beginning at the end of the stimulation slowly the previous rate of spontaneous activity was restored Did you observe this otherwise for the vestibular nonadapting system very unusual phenomenon regularly? Anyhow it should be of great interest to the ... are

develops in various ways by means of phenomena of inhibition or facilitation of the vestibular nuclear activity.

The different behaviour of the various neuronic elements of Deiters nucleus to the stimulation of the cerebral cortex may be explained on the basis of the anatomical researches by Brodal, Pompeiano & Walberg (1962) and the electrophysiological research work of De Vito, Brusa & Arduini (1956): the former have put into evidence the fact that not all the cells of the vestibular nuclei receive primary afferent vestibular fibres; the latter that the galvanic stimulation of the labyrinth may determine effects both inhibitory and facilitating on the vestibular neuron discharge and that some of these neurons anatomically belonging to the vestibular nuclei are not influenced by the labyrinthine stimulation.

Our experiments have therefore further demonstrated the validity of the hypothesis put forward by these authors to explain the different behaviour both anatomical and physiological of the neuronic units of the vestibular nuclei: these nuclei do not only represent a place of way of impulses coming from the vestibular receptors but one of the centres in which these impulses are modulated and integrated by the activity of the various centres of the nervous system.

We can therefore conclude that the modifications of the labyrinthine reflectivity due to experimental and pathological lesions of the supranuclear structures (over all the ipsilateral temporal cortex) are determined not only by an action on the ocular motoneurons and on the reticular substance but also by a direct action on the vestibular nuclei themselves.

RÉSUMÉ

Des recherches expérimentales sur le chat ont démontré les modifications suivantes de l'activité des noyaux vestibulaires: (a) la stimulation galvanique des récepteurs vestibulaires est suivie ou d'une augmentation ou d'une réduction ou d'aucun effet sur les unités deitersiennes; (b) la stimulation du lobe temporal provoque un changement de fréquence et du rythme dans les unités deitersiennes homo- et controlatérales.

ZUSAMMENFASSUNG

Experimentelle bei der Katze durchgeführte Untersuchungen haben folgende Modifikationen der Tätigkeit der Vestibulariskerne ergeben: (a) die galvanische Reizung der Rezeptoren bedingt entweder Erhöhung oder Reduktion oder keine Wirkung auf die Deitersschen Einheiten; (b) die Reizung des Temporalgebietes bedingt Veränderungen der Frequenz und des Rhythmus in den Deitersschen Einheiten der gleichen Seite sowie in jenen der Gegenseite.

REFERENCES

Adrian, E. D. 1943. Discharges from vestibular receptors in the cat. *J. Physiol.* 101, 389.

Arslan, M. 1949. Fisiopatologia del sistema supravestibolare. *Atti XXXVII Congr. Soc. Ital. Neur.* Milano.

BRODAL, A., POMPEIANO O., and WALBERG F., 1962 *The Vestibular Nuclei and their Connections Anatomy and Functional Correlation* Oliver & Boyd, Edinburgh and London

CARMICHAEL, E A., DIX, M R., and HALLPIKE C S., 1954 Lesions of the cerebral hemispheres and their effect upon optokinetic and caloric nystagmus *Brain 77*, 345

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GERNANDT B E., 1950 Midbrain activity in response to vestibular stimulation *Acta Physiol Scand*, 21, 73

GERNANDT B E., and THULIN, C A., 1955 Reciprocal effects upon spinal motoneurons from stimulation of bulbar formation *J Neurophysiol* 18, 113

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ROSSETTI S., and SALS O., 1948 Ricerche sul comportamento delle reazioni vestibolari nel coniglio dopo asportazione del telencefalo *Acta Neurologica*, 3 1

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M. Arslan (Reply): I am very grateful to Prof. *Keidel* for his remarks. The rebound of the Deitersian unit following temporal stimulation that we observed is quite similar to that observed by De Vito, Brusa & Arduini in similar preparates following cerebellar stimulation. This phenomenon is very likely produced by central interaction between structures with mutually antagonistic effect on the same neuron. The rebound effect suggests again that the temporal cortex acts upon the Deiters' nuclei through the brain stem reticular formation and that the effect is not purely inhibitory.

STAPEDIUS MUSCLE REFLEX AFTER INTERPOSITION OPERATIONS

OTTO H MEURMAN and EERO AANTAA
Turku Finland

From the Oto Laryngological University Clinic (Head Prof Otto H Meurman) Turku

The function of stapedius reflex was investigated by using the indirect method of measuring acoustic impedance when the contra lateral ear was stimulated with pure tones The material consists of 12 patients and 14 operated ears In all the cases an interposition was made and one or both of the crura of the stapes were placed on the fascia covering the window without opening the incudo stapedial joint and without cutting the stapedius tendon A positive reflex was obtained for eight ears at least at some frequencies Totally negative results were obtained in six cases The results show that a positive stapedius reflex is often possible after an otosclerosis operation in which the incudo stapedial joint and the stapedius tendon are left intact The reflex may be negative even if hearing tests show that the ossicles are mobile and normal in their function

The results also indicate that the immobility of the incudo stapedial joint and the way the stapes is fixed to the oval window are factors that influence the amount of change of impedance caused by stapedius reflex

INTRODUCTION

There are two basically different methods used in the operations for curing deafness caused by otosclerosis According to one method the stapes is replaced by a prosthesis while in the other method one or both of the crura of the stapes are preserved without opening the incudo stapedial joint and without breaking the stapedius tendon Both methods result in an equal improvement of hearing the air conduction audiogram reaches that of bone conduction audiogram The two methods are different, however as to the mechanism of the middle ear In theory at least the latter method retains the activity of the stapedius muscle

Several questions may be asked as to the latter method

1 Is stapedius reflex retained in the interposition cases in which the stapedius tendon and the incudo stapedial joint have been left intact?
2 Is the change of impedance in the middle ear, caused by a positive stapedius reflex similar in these cases and in normal ears?
3 Is the auditive function the same in a prosthesis ear and in a stapes ear ?

4. Does positive stapedius reflex protect the middle ear after the operations?

The present study is restricted to deal with the first two questions only.

MATERIAL AND METHOD

14 ears of 12 patients were operated. In each case the footplate of the stapes was removed from the oval window, the window was covered with a piece from the fascia of the temporal muscle and one or both of the branches of the stapes were placed on the fascia. The joint between the incus and the stapes was not opened and the ligament of the stapedius muscle was not cut. The primary improvement of hearing was good in all the cases, i.e. the difference between the air and bone conduction curves was minimized. The impedance measurements were performed from a couple of months to several years after the operation. Only such patients were included in the study who heard normally with the unoperated ear, or the loss was not more than 30 dB at some frequencies at least.

Stapedius muscle reflex was investigated by an indirect method by registering the changes of acoustic impedance when the contralateral ear was stimulated with pure tones. Several investigations have shown the usefulness of this method (Luscher, 1930; Lindsay *et al.*, 1936; Metz, 1946; Jepsen, 1955; Terkildsen & Scott Nielsen, 1960; Klockhoff, 1961). The present investigation was performed by using the Acoustic Impedance Meter-ZO 61 by Madsen Electronics. The control material consisting of people of normal hearing showed that the apparatus registered stapedius reflex at the intensity of 70–90 dB within the frequency range of 250–4000 cps.

RESULTS

The results are presented in Tables 1 and 2. Table 1 shows that a positive change of impedance caused by stapedius reflex was registered at some frequencies at least in eight cases, while a completely negative result was obtained in six cases. A positive result was obtained in one case at three frequencies and similarly in one case at four frequencies. The table shows further that no positive results were obtained at 250 cps.

Table 2 gives separately the results for the ears in which only one or both of the branches were preserved. The table shows that in either case both positive and negative results were obtained. The material is so small that a more detailed statistical analysis is not possible.

DISCUSSION

The results are somewhat surprising in certain respects. It was expected that stapedius reflex was positive in all the present cases because the tendon was not broken, because the incudostapedial joint was not opened,

TABLE 1 *Changes of impedance at various frequencies*

Case	250	500	1000	2000	4000
A A dx	–	–	–		–
sin	–	+	+	+	+
K J		–	–	–	–
S B	–	–	–		+
K B	–	–	+	+	+
N M	–	–	–	–	–
J A	–	–	–		–
S K		–	+	–	–
S L dx	–	–	+	+	–
sin	–	–	+	+	–
K M	–	–	–		–
Z L		–	–		+
H J	–	–	+	–	–
S J	–	–	–	–	–

and because of the audiograms showed a good connection between the ossicles and the oval window and a good sensitivity of the ossicles to vibrations. A positive stapedius reflex *is an indication of a normal function of the ossicles.* Some investigators, however, have presented exceptions to this general rule. So for example *Klockhoff* mentions a case in which the reflex was positive even if the connection between the ossicles was broken because the *crura* were traumatically disconnected from the footplate of the stapes.

In the present material there are however several negative results. It seems appropriate to consider the possible causes of the *negative results more closely. Probably* the most common cause for the non existence of stapedius reflex when the ossicles are mobile is that the sound stimulus to the contralateral ear is not strong enough. The present material was chosen so *that* the contralateral ear could be stimulated in all *the cases with a* sound *over at least 70 dB* often over 90 dB. Sounds of the highest intensities *however*, were not reached in all the individual cases and all the frequencies and therefore the negative results may in some cases *but not in* all depend on the insufficient intensity level of *the sine waves*. Another relevant factor *is no doubt*, the incudo stapedial joint and the mobility of the *stapes. It is a* well known fact that the *structure particularly the firm*

TABLE 2 *Changes of impedance*

	+	–
One crus	5	4
Both crura	3	2
Total	8	6 = 14 cases

4. Does positive stapedius reflex protect the middle ear after the operations?

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DISCUSSION

The results are somewhat surprising in certain respects It was expected that stapedius reflex was positive in all the present cases because the tendon was not broken, because the incudostapedial joint was not opened,

1. When the incudo stapedial joint and the stapedius tendon are left intact in an otosclerosis operation it often happens that a positive stapedius reflex is obtained after the operation. The reflex may sometimes be negative even if hearing tests show that the ossicles are mobile and operate normally.
2. The immobility of the incudo stapedial joint and the way the stapes is fixed to the oval window are additional factors that affect the change of impedance caused by stapedius reflex.

RÉSUMÉ

L'investigation veut examiner la question si le reflexe stapedien est positif après l'opération d'interposition dans les cas où l'on sauvegarde les branches de l'étrier et le tendon du muscle de l'étrier. On discute les resultats.

ZUSAMMENFASSUNG

Die Funktion des Stapediusreflexes wurde durch ein indirektes Messungsverfahren der Impedanz untersucht, wobei das *kontralaterale Ohr durch reine Töne* gereizt wurde. Das Untersuchungsmaterial lieferten insgesamt 14 operierte Ohren von 12 Patienten. An allen war eine Interpositionsoperation durchgeführt worden, wobei der eine oder beide Stapesschenkel der das Fenster bedeckenden Faszia aufgelegt wurden, ohne Öffnung des Incudostapedialgelenks und ohne *Durchschneiden des Stapediustends. Es wurde in 8 Fällen ein positiver* Reflex auf zumindest einem Frequenzbereich erzielt. Ein völlig negatives Resultat ergab sich in 6 Fällen.

Die Ergebnisse lassen erkennen, dass die Erhaltung des Incudostapedialgelenks und des Stapediustends bei Otosklerosoperationen in vielen Fällen einen positi*ven Stapediusreflex ermöglicht. Der Reflex kann auch negativ ausfallen, obgleich* die Ergebnisse einer Untersuchung des Hörvermögens auf eine gut wirkende *mobile Gehörkette hinweisen.*

Die Ergebnisse weisen auch darauf hin, dass sowohl die Festigkeit des *In*cudostapedialgelenks als auch das Aufliegen des Stapes auf dem ovalen Fenster *auf den* Umfang der durch einen Stapediusreflex verursachten *Impedanzveränderung einwirken.*

REFERENCES

Jepsen, O., 1955. Studies on the *acoustic stapedius reflex in man. Thesis.* Universitetsforlaget, Aarhus.

Klockhoff, I., 1961. *Middle ear muscle reflexes in man. Acta Otolaryng. (Stockh.)* Suppl. 164.

Lindsay, J. R., Kobrak, H., and Perlman, H. B., 1936. Relation of the stapedius reflex to hearing sensation in man. *Arch. Otolaryng.* 23, 671.

Lüscher, E., 1929 *a*. Die Funktion des Musculus Stapedius beim Menschen. *Z. Hals- Nas- Ohrenheilk.* 23, 105.

— 1930 *b*. *Z. Hals- Nas- Ohrenheilk.* 25, 462.

Metz, O., 1946. The acoustic impedance measured on normal and pathological ears. *Acta Otolaryng. (Stockh.)* Suppl. 63.

Terkildsen, K., and Scott Nielsen, S., 1960. An electroacoustic impedance measuring bridge for clinical use. *Arch. Otolaryng.*, 2, 339.

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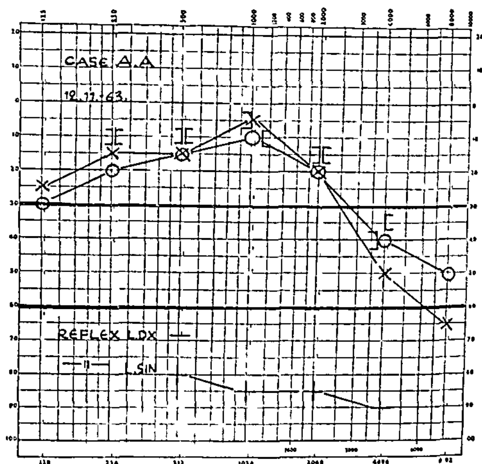


Fig 1

ness, of the joint varies considerably During operations it is possible to see that in some cases the joint between the stapes and the processus lenticularis is very mobile while in other cases it may be rather firm and immobile The mobility of the stapes in relation to the incus depends not only on the mobility of the joint but also on the way the crura are fixed to the membrane covering the window If there is only one crus the stapedius muscle is likely to move the stapes more than in the case where both of the branches are firmly fixed to the footplate or the fascial tissue replacing it In the latter case the stapes has a stronger influence on the movements of the incus Therefore it is possible that a stapes that easily moves sideways has a smaller influence on the change of acoustic impedance than a stapes which, even if mobile, does not move sideways so easily This theory is supported by our case No 1, in which a positive reflex was obtained in the ear in which both of the crura were normal in length, while there was no reflex in the ear that had only the posterior crus left A positive stapedius reflex in those cases where only one crus was left is probably an indication of a relatively immobile incudo-stapedial joint and a certain kind of fixation between the stump of the other crus and the window

The following two conclusions can be drawn on the basis of the present study

tion. To gain information of the prognosis, a follow-up study was conducted on all the patients, on most of them more than two years after the onset of the disease.

When dealing with the role of psychologic factors in Meniere's disease, we must try to determine the way in which the symptoms of the disease are related to various life stress situations Naturally, it is important here to note whether the vertiginous attacks started at a time when the patient was exposed to stress, but in addition the later relationship between the attacks and stress should be studied We have also tried to find out the part played by summation of various stresses in the degree of Meniere symptoms

An evaluation of the correlation between stress and disease presupposes a determination of the degree of stress—some sort of "measurement". In the disease concerned, we have regarded vertigo as the principal criterion, viz as the symptom by which to assess the degree and progress of the disease, as well as recovery

It is extremely difficult to appraise the degree of stress. Yet on the basis of a consistent assessment by a psychologist with many years' experience, it seems we have arrived at a classification suitable for our purposes and so are able to approach the problem under study. For as clear a picture as possible to be obtained of both the psychic and the somatic status of the patients, they were subjected to careful physical examination and, from confidential interviews, the psychologist of our hospital (Siltala) formed her opinion on their psychic anamnesis. The results were grouped into six categories:

1 Childhood
2 Marriage
3 Emotional status
4 Difficulties at work
5 Financial status and social relations
6 Other diseases

1 Security in childhood environment.

2 Marriage (in cases in which the patient was or had been married). The interrelationships of family members, divorce, death, infidelity, and children Eight of the patients were unmarried, this represents about 20 per cent, in itself a high proportion.

3 Emotional status, which term here covers possible psychic abnormality, emotional pattern, human relationships, life rhythm, feeling of security, sleep, use of alcohol, ambitions, religious revivals, etc.

4 Circumstances at work, including morale in working place, physical and mental strain, continuity of work, unemployment, and job satisfaction.

5 Social status, here including financial situation, living quarters, social relations and contacts, etc

6 Other, chiefly somatic diseases

PSYCHOLOGICAL ASPECTS OF MENIÈRE'S DISEASE

Preliminary report

URPO SIIRALA, PIRKKO SILTALA and JAAKKO S LUMIO
Helsinki, Finland

Forty-three patients with Menière's disease were chosen at random from hospital case material. They were subjected to analysis of the personality pattern on the basis of observations from interviews and of the Rohrschach test.

It appeared that the degree of psychic stress present was especially marked at the time the disease started. In those patients who were cured and free from attacks of vertigo, the degree of stress was also less By contrast, in the patients who were not cured, various life stresses of very marked degree were still present at follow up The stresses due to emotional factors and to difficulties at work and in marriage were the most severe Accumulation of various stresses to form a severe total of stress occurred most frequently in the group of patients who were not cured.

The part played by psychic factors in the origin of Menière's disease is difficult to evaluate Several reports have been published of cases with Menière attacks preceded by an emotional stimulus Thus Fowler & Zeckel (1953) have emphasized the role of life stress situations in the attacks of vertigo in Menière's disease According to them there is apparently a fundamental emotional predisposition, which causes the attacks as a reaction in stress situations Among the several psychologic factors in the attacks Fowler lists personal antagonism, sexual abstinence, sexual conflicts, death of a near relative, and various other life stresses He says "it is impossible not to conclude that Menière's disease of the typical paroxysmal type most assuredly has a psychic etiology"

Ceroni & Franzoni (1963) observed, in 44 per cent of a group of 50 patients, a relationship between emotional stimulus and onset of the crisis They suggest that "the peculiar somatization of the psychic troubles depends not so much on the contents of the troubles, but specially on a previous state of functional weakening of the organ of hearing"

Since our patients included several with psychic disturbances apparently related to Menière's disease, we deemed it advisable to study the importance of these factors more closely Our study was carried out with the objective of evaluating the personality pattern of Menière patients on the basis of observations from interviews and of the Rohrschach test, keeping in view the possible correlation between life stresses and symptoms of this condi-

tion

on ...

the disease

When dealing with the role of psychologic factors in Meniere's disease, we must try to determine the way in which the symptoms of the disease are related to various life stress situations Naturally, it is important here to note whether the vertiginous attacks started at a time when the patient was exposed to stress, but in addition the later relationship between the attacks and stress should be studied We have also tried to find out the part played by *summation of* various stresses in the degree of Meniere symptoms

An evaluation of the *correlation between* stress and disease presupposes a determination of the degree of stress—some sort of "measurement" In the disease concerned, we have regarded *vertigo as the principal criterion*, viz as the symptom by which to assess the degree and progress of the disease, as well as recovery

It is extremely difficult to appraise the degree of stress Yet on the basis of a consistent assessment by a psychologist with many years' experience, it seems we have arrived at a classification suitable for our purposes and so are able to approach the problem under study For as clear a picture as possible to be obtained of both the psychic and the somatic status of the patients, they were subjected to careful physical examination and, from confidential interviews, the psychologist of our hospital (Siltala) formed *her opinion on their psychic anamnesis* The results were grouped into six categories

1 Childhood
2 Marriage
3 Emotional status
4 Difficulties at work
5 Financial status and social relations
6 Other diseases

1 Security in childhood environment

2 Marriage (in cases in which the patient was or had been married) The interrelationships of family members divorce, death, infidelity, and children Eight of the patients were unmarried this represents about 20 per cent, in itself a high proportion

3 Emotional status, which term here covers possible psychic abnormality, *emotional pattern*, human relationships, life rhythm, feeling *of security*, sleep use of alcohol, ambitions, religious revivals, *etc*

4 Circumstances at work, including morale in working place, physical and mental strain, continuity of work, *unemployment*, *and job* satisfaction

5 Social status, here including financial situation, living quarters, social relations and contacts, etc

6 Other, chiefly somatic diseases

PSYCHOLOGICAL ASPECTS OF MENIÈRE'S DISEASE

Preliminary report

URPO SIIRALA, PIRKKO SIITALA and JAAKKO S LUMIO
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Forty-three patients with Meniere's disease were chosen at random from hospital case material. They were subjected to analysis of the personality pattern on the basis of observations from interviews and of the Rohrschach test.

It appeared that the degree of psychic stress present was especially marked at the time the disease started. In those patients who were cured and free from attacks of vertigo, the degree of stress was also less By contrast, in the patients who were not cured, various life stresses of very marked degree were still present at follow up The stresses due to emotional factors and to difficulties at work and in marriage were the most severe Accumulation of various stresses to form a severe total of stress occurred most frequently in the group of patients who were not cured

The part played by psychic factors in the origin of Meniere's disease is difficult to evaluate Several reports have been published of cases with Meniere attacks preceded by an emotional stimulus Thus Fowler & Zeckel (1953) have emphasized the role of life stress situations in the attacks of vertigo in Meniere's disease According to them there is apparently a fundamental emotional predisposition, which causes the attacks as a reaction in stress situations Among the several psychologic factors in the attacks Fowler lists personal antagonism, sexual abstinence, sexual conflicts, death of a near relative, and various other life stresses He says "it is impossible not to conclude that Menière's disease of the typical paroxysmal type most assuredly has a psychic etiology"

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Since our patients included several with psychic disturbances apparently related to Meniere's disease, we deemed it advisable to study the importance of these factors more closely Our study was carried out with the objective of evaluating the personality pattern of Meniere patients on the basis of observations from interviews and of the Rohrschach test, keeping in view the possible correlation between life stresses and symptoms of this condi-

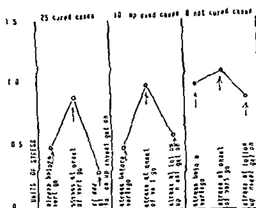


Fig 1 Average values of psychological stress Difficulties in marriage

tern roughly as follows The Menière patient's ego is so weak that he cannot cope with excessive tensions and external stress situations, he cannot make use of his inner resources and integrate the affective impulses into his personality, this results in psychosomatic reactions

We have here used a specific "Unit of Stress" in an attempt to show graphically the variations in stress and its relationship to Menière's disease Although the use of such a method in the "measurement" of psychic phenomena may with some reason be considered strange, it seems to offer a means to objectify the degree and variation of the psychological difficulties studied by us

A Unit of Stress (U S) here denotes a *disturbing* degree of stress, while the rating two Units of Stress has been considered to represent *excessive* stress Our results will be considered below in terms of this 'Unit of Stress'

Fig 1 shows the average degree of stress due to *marital difficulties* in the cured and improved cases, and in those not cured It is found that a typical peak in average degree of stress occurs at the time of the onset of disease

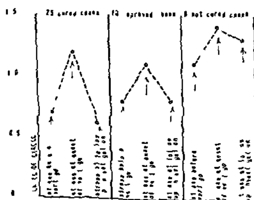


Fig 2 Average values of psychological stress Emotional difficulties

The series consists of 43 Menière cases chosen at random among 62 hospitalized patients treated at the Helsinki University Otolaryngological Hospital, during the years 1960–62. The sex distribution was 19 men and 24 women. The majority of the patients were in the age range 30–60 years

The psychologist tried to discover especially the various stress factors occurring during childhood, before the disease, at the time of onset, and during the follow-up investigation, which was made in most cases more than two years after the appearance of symptoms

The patients were divided into three groups: (1) those who no longer had any vertiginous attacks (cured), (2) those who were essentially improved but still were suffering from some degree of giddiness (improved), and (3) those in whom disease continued and attacks persisted (not cured)

The results would seem to show that stress in childhood bears no relationship to the tendency to cure in Menière's disease However, those under severe stress in childhood seemed in their later life also to be exposed to various stresses emotional trauma in childhood apparently resulted in emotionally and psychologically disturbed and vulnerable individuals

The patients studied included none who was not or had not been subject to psychic stress of some sort, though it was fairly slight in a few cases In most of the "stress categories", the stress had been most intense at the time of onset of the disease During the time preceding the onset of symptoms and for a few years afterwards stress was generally found to be less severe, but the attacks of vertigo and the degree of stress show a definite correlation When attacks grow milder and fewer or disappear, the stress is also slighter On the other side, in the cases in which attacks continue, the stress is later the same or only slightly less than at the time of the onset of the disease Naturally enough, Menière's disease itself causes severe stress, and one may ask which of the two is really the cause and which the effect Where the stress has been present before the onset of symptoms and when the disease breaks out at the time the stress is greatest, it is impossible not to think that the stress is the primary factor

On the other hand, six patients had been subjected to a destructive operation on the labyrinth by the method of Cawthorne All these patients got rid of their vertigo and their stress was also found to be much less at follow up It is not very likely that in all these cases the stress would have decreased as it were "by chance" after operation More probably the postoperative disappearance of attacks of vertigo had eased the patients' condition so much as to cause psychic rehabilitation of a kind and relief of stress in various life situations It would seem that the stress and the Menière symptoms initiated by it, set up a kind of vicious circle, each aggravating the other Escape is only possible by interrupting the circle as vertigo disappears, the stress is relieved, and where stress is less there is no longer any vertigo

It should be emphasized that the Menière patients concerned were emotionally disturbed Indeed our psychologist described their personality pat-

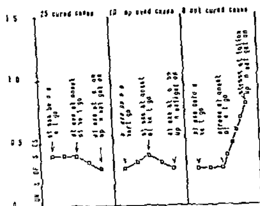


Fig 5 Average values of psychological stress Other diseases

with the above factors, however, in the group of those not cured the stress, on an average relatively slight, is still of the same degree as at the time of onset

The stress caused by *other additional diseases* has been fairly slight in the patients studied (Fig 5) Particular interest is aroused by the fact that the progress of Meniere s disease in the not cured patients is associated with various additional troubles and diseases

Accumulation of stress, viz the simultaneous occurrence of various life stresses seems to affect Meniere s disease unfavourably Using the Unit of Stress to illustrate this matter (Table 1), it is seen that the total sum of various life stresses shows a maximum at the onset of Meniere s disease but at follow up a considerable decrease in the groups of improved and cured In the group in which attacks of vertigo still occur, the total sum of stresses also remains at a high level

Most significant from the point of view of the course of Meniere s disease seems to be an abnormal psychosomatic constitution which expresses it self as emotional difficulties For this reason perhaps the difficulties at work are also particularly great Third in order of importance are the stress factors in marriage *Social difficulties and other diseases seem to be* of less importance, apart from the fact already mentioned, that patients with prolonged Meniere s disease tend to develop additional diseases and troubles

TABLE 1 *Summation of stress*

The average summation of life stress in the five different categories investigated (expressed in Units of Stress)

No of patients	Cured 25	Improved 10	Not cured 8
Before onset of M disease	2 4 U S	2 6 U S	3 8 U S
At onset of M disease	4.3 U S	4 5 U S	4 8 U S
At follow up	1 6 U S.	2 0 U S	4 8 U S

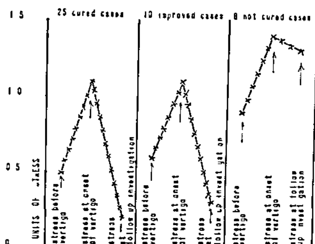


Fig 3 Average values of psychological stress Difficulties at work

(the average stress being 1 U S) Follow-up results show that the stress in the cured patients has decreased to a fairly low level, in those who improved it is considerably less than at the time of onset of disease, whereas in those not cured the stress, though slightly less than at the onset of disease, continues to be relatively great (0 9 U S)

Fig 2 illustrates the *emotional status* in the three groups of patients The degree of stress at the time of onset of symptoms averages more than one U S , in the group of patients not cured almost one and a half U S As can be seen from the curves, the stress in the patients not cured continues and at follow up is of almost the same degree of severity as during the onset of Menière attacks

Fig 3 indicates the stress due to *difficulties at work* Here, too, the stress is most severe at the onset of the disease and is shown on follow up to be slighter in the cured and improved groups, but in the case of those not cured severe stress is still present at follow up

Social difficulties (Fig 4) are evidently of minor importance compared

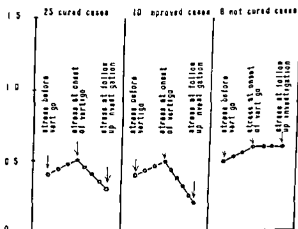


Fig 4 Average values of psychological stress Social difficulties

ZUSAMMENFASSUNG

ine Gruppe von Meniere Patienten wurde psychologisch analysiert Die Re ate dieser Analysei werden vorgelegt Gewisse psychische Faktoren sind of par aetiologisch bedeutungsvoll bei dieser Krankheit

REFERENCES

SLER I P., JR., and ZECKEL, A., 1953 Psychophysiological factors in Meniere's disease *Psychosom Med* 15 127
ONI T., and FRANZONI M., 1963 Aspetti psicosomatici della malatia di Meniere *Ann Laring (Ter)* 4 306

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DISCUSSION AND CONCLUSIONS

Thus it seems that in patients with a certain psychosomatic constitution Meniere's disease can develop on the basis of emotional stress. On this point the writers agree with Fowler and Zeckel, Ceroni and Franzoni, etc. A lessening of stress was found to be associated with relief of vertigo. When stress continued to be severe, the vertiginous attacks also continued. Accumulation of various life stresses seemed to be of importance in rendering the prognosis more grave: the total sum of stresses was somewhat greater in the group of patients not cured than in the cured and improved groups, and the stress continued as the disease progressed.

All the six patients subjected to a destructive operation on the labyrinth were cured. The disappearance of vertiginous attacks after operation was associated with a lower degree of stress. It would seem that in these and also in many conservatively treated cases the vicious circle referred to above was interrupted, and treatment opened a road to emotional rehabilitation, to which improved working capacity seems to have contributed essentially.

Special interest should be directed to Meniere patients who appear to be under psychic stress. These require help in their personal problems: resolution or relief of problems and conflicts may decisively influence the prognosis. (But operative therapy and medication also seem to be of great help in suitable cases.)

This preliminary report has many shortcomings. It lacks a control material illustrating the normal occurrence of stress. It was not possible to a sufficient extent to consider the variations in stress in the surgically treated group, since the series included so few patients operated on. A number of other questions still remain unanswered. It is our intention to continue these studies and as far as possible subject all our Meniere patients to psychological study. However, we have wished to report the observations hitherto made and the opinion reached from our results: when the sum of life stresses exceeds the tolerance limit of a patient, he can—when constitutionally predisposed—develop symptoms of Meniere's disease, which seem to continue as long as the stress is severe. This parallelism is indicative of a causal correlation.

ACKNOWLEDGMENT

The financial support of Ane Gyllenbergs stiftelse is gratefully acknowledged.

RÉSUMÉ

Un groupe de patients souffrant de maladie de Menière ont été analysés psychologiquement. Les résultats de cette analyse sont exposés. Certains facteurs psychologiques semblent être particulièrement importants dans le développement de cette maladie.

the anterior part of the nasal mucous membrane of the septum around the junction with the squamous epithelium *rather spongy and containing* numerous duct openings from this gland system. Thus for the first time it was established that this gland system existed in the human nasal mucous membrane too.

In the film is seen Steno's original illustration *of the lateral nasal gland, the beautiful wax preparations* of the anterior nasal glands of professor Broman, some osmium-acid fixed preparations from rats, rabbits and monkey and some cadaver preparations from the anterior part of the nasal mucous membrane on the septum along with some wholemount preparations fixed in osmium acid from the *human nasal membrane* showing this gland system and their ducts. Finally some movie pictures of this area are shown, demonstrating not only the drops of fluid along with the crypt openings, but also that in some cases of human beings a movement of these fluid drops can be seen synchronous with the respiration, that is that the *drops project during inspiration and disappear into the* ampulli or the ducts during expiration. The film ends with a model experiment where one can see that during inspiration these fluid drops may be sucked up into the olfactory region indicating that these drops beyond humidification of the *nasal mucous membrane might have something to do with the sense of* olfaction.

RÉSUMÉ

1662 entdeckte und beschrieb Nicolaus Steno die laterale Nasendrüse am Tier. *1918 l'anatomiste suédois Broman* décrit quelques glandes nasales médiales sans tirer attention. Ces glandes nasales médiales étaient découvert *de nouveau en 1963* wiederentdeckt und nun auch beim Menschen.

ZUSAMMENFASSUNG

1662 entdeckte und beschrieb Nicolaus Steno die laterale Nasendrüse am Tier. *1918* entdeckte der schwedische Anatome Broman einige mediale Nasendrüsen im *Tier, aber ohne Aufmerksamkeit zu wecken. Die letztgenannten* Drüsen wurden *1963* wiederentdeckt und nun auch beim Menschen.

REFERENCES

BOJSEN-MØLLER, F. Topography *of the nasal glands in rats and some other mammals. Anat. Rec.* (in press).

— Glandulae nasales anteriores in the human nose. *Ann. Otol.* (in press).

BROMAN, IVAR, 1918. *Om Jacobsonska* organets konstruktion och *funktion. Year-book of the University of Lund* 14, 1–43.

STENO, N. *Observationes anatomicae*, quibus varia oris, oculorum et narium vasa describuntur novique salivae, lacrymarum *et muci fontes deteguntur*. Lugduni Batavorum, IV 1662.

Oslo Plads 14, Copenhagen, Denmark

FILM: ANTERIOR NASAL GLANDS

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Nicolaus Steno in 1662 discovered and described the lateral nasal gland in animal. In 1918 the Swedish anatomist Broman discovered the medial nasal gland in animal without attention being paid to it. 1963 these nasal glands were rediscovered and also in man.

In 1963 a young Danish anatomist, Dr. F. Bojsen-Møller, was occupied in making wholemount preparations of the nasal mucous membrane in animals. This purpose was to obtain a survey with regard to later election microscopical studies. The specimens were taken from the septum of the nose and were fixed in osmium tetraoxide. Having made the preparations translucent he examined them microscopically, and to his surprise he found between the Broman glands upwards and backwards and Jacobson's organ downwards and forwards a system of numerous serous glands forming long convoluted ducts that ended up just behind the vestibule of the nose. This gland system apparently had not been described before neither by anatomists nor by rhinologists. We knew that the Danish anatomist Nicolaus Steno in 1662 had described what he called a lateral nasal gland in sheep and dog. Later on it was eventually found out that the Swedish anatomist Ivar Broman in 1918 had published some investigations on Jacobson's organ in animal, and as a by-product to this he had found beyond the lateral gland of Steno a gland system on the septum of the nose, and furthermore he had made some beautiful wax preparations of these gland systems. These wax preparations were found as photographs whereas the original wax preparations had been destroyed. Obviously this gland system described by Broman and the gland system discovered by Bojsen-Møller is exactly the same. However, the investigations of Broman were not paid attention to so that one really could say that Dr. Bojsen-Møller had rediscovered these glands in animal.

When he came to us to demonstrate these preparations and to ask us whether we knew about these gland systems, we had to admit that we did not know them, and to our knowledge neither Negus nor Proetz had ever mentioned these glands.

Having seen the preparations of Dr. Bojsen-Møller we found it obvious to place him on an examination table and to examine his nasal septum mucous membrane, and here we not only found several drops of serous fluid as many rhinologists probably have seen it before, but also we found

DER STAPEDIUSREFLEX DES WACHEN KANINCHENS AUF TONREIZE MITTLERER LAUTSTÄRKE

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Würzburg, Deutschland

Aus der Universitäts-Hals-Nasen-Ohren-Klinik Würzburg (Dir.: Prof. Dr. H. L. Wullstein)

Eines der Hauptthemen dieser Tagung ist die Verarbeitung von akustischen Reizen durch die zentralnervösen Anteile des Gehörorganes gewesen. Wir haben gesehen, wie fruchtbar dabei die an der Informationstheorie geschulte Betrachtungsweise geworden ist. Ich möchte nun mit einem Ausflug in die *Reflex-Physiologie der Mittelohrmuskeln* zu zeigen versuchen, wie schon dieser dem Sinnesorgan vorgeschaltete Apparat *zur Verbesserung der Informationsübertragung* beisteuert.

Seit den klassischen Arbeiten von v. Helmholtz (1868), Tsukamoto (1930), Lindsay, Kobrak & Perlman (1936), Lorente de Nó (1935) und Wiggers (1937) und vieler anderer sind wir an die Auffassung gewöhnt, daß die Mittelohrmuskeln eine dämpfende Wirkung auf die Gehörknöchelchenkette ausüben und deshalb 1.) das Ohr vor überlautem Schall schützen und 2.) in höheren Frequenzen den Klirrfaktor vermindern (Ranke 1953). Ausschlaggebend hierfür war die Erfahrung gewesen, daß der Reflex erst mit hohen Lautstärken des Tonreizes hervorzurufen war. Fischer hat dann erstmalig am Menschen beobachtet, wie sich die Steigbügelsehne auch auf geringere Schallstärken hin bewegte. In letzter Zeit ist vor allem von Galambos, Simmons (1959) und von anderen mit der Galambosschen Technik arbeitenden Forschern (Carmel & Starr 1963) darauf hingewiesen worden, daß der Reflex auch durch mittlere Lautstärken und vor allem auch durch nichtakustische Reize im Tierexperiment auslösbar ist.

In Verfolgung des Problems, ob im Stapediusmuskel Propriorezeptoren vorhanden sind, hatten Herr Brauer und ich Anfang des Jahres bestätigen können, daß schon Tonreize von 40 bis 50 Dezibel über der menschlichen Hörschwelle ausreichen, um Muskelaktionspotentiale im Stapedius des wachen Kaninchens hervorzurufen. Propriorezeptoren im Stapedius sind von manchen Anatomen (Bargmann 1951) mitgeteilt worden; uns war an ihrem elektrophysiologischen Nachweis gelegen. Zu diesem Zweck hatten wir unter Ausnutzung eines besonderen Zugangsweges feine Makroelektroden an verschiedenen Stellen des Reflexbogens nichtanästhesierter Kaninchen angelegt und dann registriert, was auf Tonreize und auf elektrische Reize des Nervus stapedius erfolgte. Im ersten Diapositiv sehen Sie, wie man vom Mastoid aus, ganz ähnlich wie bei der Facialis-Dekompressionsoperation nach Wullstein (1958), auf die Oberseite des Stapediusmuskels

DISCUSSION

G. de Wit My congratulations on the rediscovery of these glands of Steno In aviation the tube of Venturi is in use. The nose is very likely such a Venturi tube. It begins wide (vestibulum), narrows (isthmus) and widens again For such a system the law of Bernoulli holds good which says that the sum of static and dynamic pressure is constant. In the narrowest place the dynamic pressure raises, so the static pressure has to lower. This is indeed what happens The static pressure lowers in the isthmus about 20 mm water. We have seen this in the beautiful film of Kristensen that during inspiration the drops of thin mucus are pressed out of the glands Perhaps this is one of the means to moisten the air during inspiration.

H K Kristensen (Reply) to *Dr de Wit* We are quite aware of the pressure changes in the isthmus area, where the duct openings of this gland system are found—and maybe this is very important as far as humidification of the inspired air is concerned. However, it is difficult to determine the role of these glands in this respect because beyond this system also the mucous glands may contribute and finally the condense water from expiration may play a very important role as is evident from the saving in loss of water by employing the "artificial nose in tracheotomized patients The function of these glands remains to be solved in future times, this presentation was meant as food for thought

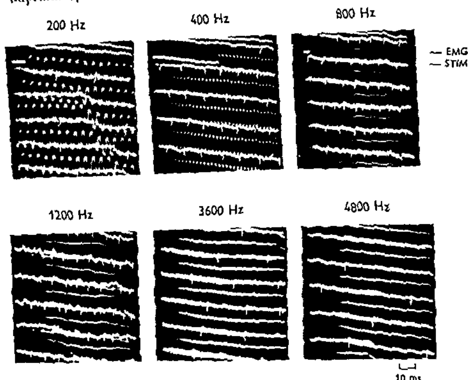


Fig. 2. Frequenzabhängigkeit von Latenzzeit und Entladungsrate einer motorischen Einheit des Musculus stapedius. Erläuterung im Text. Zeilenschrift

wie eine motorische Einheit erst bei der Mindestfrequenz von 100 Hz *zu* feuern beginnt und bereits bei 6000 Hz ihre *Tätigkeit wieder* einstellt. Die *optimale* Reizfrequenz liegt nach unseren Erfahrungen zwischen 800 Hz und *2000 Hz*, höhere Frequenzen als 6000 Hz wurden hier nicht beantwortet. Auf den Bildern ist vor allem bemerkenswert, wie sich die Latenzzeit *des Auftretens und die Entladungsrate* der motorischen Einheit mit der Reizfrequenz ändern: beide weisen Minima bzw. Maxima bei etwa 1200 Hz auf.

Wie empfindlich manche motorischen Einheiten eine bestimmte *Frequenz* beantworten, zeigt vielleicht besser als viele Worte ein kurzer *Tonbandstreifen* mit einer akustischen *Demonstration*. Hier sind gleichzeitig hör- und sichtbar die Microphonics (Ableitung vom runden Fenster) *und die Aktionspotentiale des Stapediusmuskels*.

IV. Registriert man gleichzeitig die Microphonics am runden Fenster, den Reiz und die Reflexaktivität im Stapedius, so kann man beobachten, wie gleichzeitig *mit dem Auftreten von Aktionspotentialen die Amplitude der Schwingungen am runden Fenster* abnimmt. Von Carmel & Starr liegen dazu Mitteilungen vor, man darf *wohl diese* Dampfung als Wirkung des Muskelreflexes, der den Steigbügel *fesselt*, betrachten. Ich bringe auch hierzu ein Beispiel (Fig. 3), das *allerdings* nicht sehr viel Verminderung der Am-

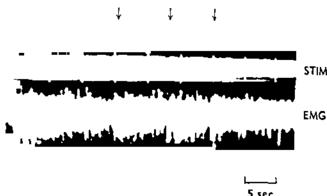


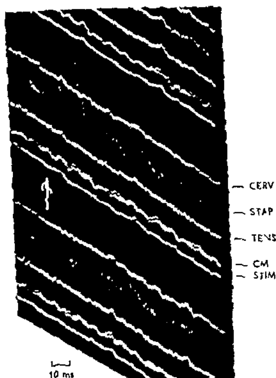
Fig. 1. Frequenzwechsel läßt den Stapediusreflex nicht ermüden. STIM = Dauerton von 1000 Hz, der dreimal (Pfeile) um 200 Hz erhöht wird. EMG: Aktionspotentiale des Musculus stapedius.

gelangt und hier den Stapediusnerven freilegen kann. Anschließend an diese Ohroperation wurden die Tiere künstlich beatmet und im Halsmark hinter C 1 durchtrennt.

I. Es zeigte sich nun bei der *elektrischen Reizung des Stapediusnerven* mit Rechteckspannungen ansteigender Intensität, daß die Latenzzeit zwischen Reiz und Muskelzuckung unabhängig von der Intensität konstant blieb. Diese Konstanz der Latenzzeit legt nahe, daß es sich nur um indirekte Muskelzuckungen handelte, nicht dagegen um die Auslösung eines sog. H-Reflexes, d. h. elektrische Reizung der afferenten Fasern aus Muskelspindeln. Bei Vorhandensein afferenter Fasern im Stapediusnerven hätte es nämlich einen Latenzzeitsprung geben müssen, wie wir es von Paul Hoffmann wissen, und wie es z. B. eine gleichartige Reizung eines gemischtmotorischen Nerven zeigt, hier des N. Ischiadicus eines Kaninchens. Diese elektrophysiologische Argumentation gegen das Vorhandensein von Propriorezeptoren im Stapediusmuskel mit afferenter Leitung über den Stapediusnerven stimmt überein mit morphologischen Studien von v. Brzezinski in Greifswald und von Jan Wersäll. Arslan hat kürzlich die Meinung vertreten, daß Afferenzen vom Stapediusmuskel über den Nervus tympanicus, also über einen Ast des Glossopharyngicus, verlaufen.

II. Die Prüfung auf *Ermüdbarkeit des Stapediusreflexes* hatte folgendes Ergebnis. Bei Reizung mit einem Dauerton bestimmter Frequenz kann man oft den schon von Eliasson & Gisselsson beschriebenen zyklischen Rückgang der Stapedius-Aktivität beobachten. Dreht man jedoch während der Dauerreizung die Frequenzskala durch, dann bleibt die volle Reflexaktivität erhalten, wie das nächste Bild zeigt (Fig. 1). Wir dürfen demnach die Erscheinung der Reflexermüdbarkeit nicht auf den motorischen Schenkel, sondern allein auf den sensorischen Schenkel des Reflexbogens beziehen, genauer wohl auf die Adaptation des Gehörs zurückführen.

III. Aber nur in einem *bestimmten Frequenzbereich* kann man solche massiven Entladungen erwarten. Die folgenden zwei Bilder (Fig. 2) zeigen,



Fi[illegible] Impulsfolgen von 50 sec (STIM) mit etwa 100 dB über der Schwelle rufen heftige Entladungen des Musculus stapedius (STAP) hervor. Das Interferenzmuster ist vom Kathodenstrahl nicht hell genug nachgezeichnet. Der Pfeil bezeichnet den Beginn der maximalen Entladung. Die Ausschwingvorgänge am runden Fenster (CM) sind zu diesem Zeitpunkt auf weniger als 20 msec verkürzt. Geringe Reflextätigkeit im Musculus tensor tympani (TENS). Der Halsmuskel (CERV) bleibt in Ruhe.

plitude zeigt. Bei allen bisherigen Beobachtungen resultierte eine Verkleinerung auf nur weniger als die Hälfte. Das bedeutet im Geltungsbereich des Hookeschen Gesetzes (Auslenkung proportional zum Druck) eine Dämpfung von weniger als 6 Dezibel. In den Bildern von Carmel & Starr beläuft sich diese Amplitudenverkleinerung auf gleiche Werte. — Wenn wir auch berücksichtigen müssen, daß es sich beim Aufzeichnen der Microphonics um stark von den Elektrodeneigenschaften abhängige Zeitabläufe handelt, dürfen w[illegible] ... ius reflex [illegible] ... als Schutz [illegible] nur ernsthaft in Betracht kommt. Ich darf diese Überlegungen hier nur streifen und möchte Ihnen abschließend mit einigen Diapositiven meine Auffassung entwickeln, daß der Wert des Stapediusreflexes viel mehr in der

A. Dämpfung von Ausschwingvorgängen zu suchen ist. Nimmt man als akustischen Reiz einmal nicht Töne, sondern Impulse, so kann man den

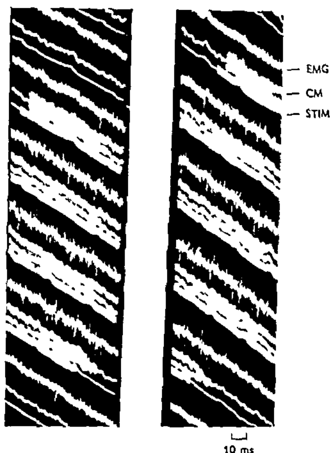


Fig. 3. Die Reizung mit einem Dauerton von 1200 Hz führt zu massiven Entladungen des Musculus stapedius (EMG), aber nur zu einer geringfügigen Amplitudenminderung der Schwingungen der runden Fenstermembran (CM). Zeilenschrift von zwei Reizungen.

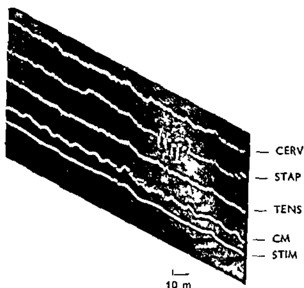


Fig. 4. Ein einzelner Impuls (STIM) von etwa 100 dB über der Schwelle ruft einen Ausschwingvorgang der Membran des runden Fensters (CM) von etwa 30 msec Dauer hervor. Er wird vom Musculus stapedius (STAP) mit einer Salve von Aktionspotentialen beantwortet. Tensor Tympani (TENS) und ein Halsmuskel (CERV) schweigen.

L'effet du reflexe sur l'attenuation des oscillations de la fenetre ronde prefere la reduction temporale des oscillations transitoires mieux que la reduction des amplitudes.

LITERATUR

Arslan, M., 1960. The innervation of the middle ear. *Proc. Roy. Soc. Med.* 53, 1068.

Bargmann, W., 1951. *Histologie und mikroskopische Anatomie des Menschen.* II. Band, S. 463. G. Thieme Verlag, Stuttgart.

Carmel, P. W. und Starr, A., 1963. Acoustic and nonacoustic factors modifying middle ear muscle activity in waking cats. *J. Neurophysiol.*, 26, 598.

Eliasson, S. und Gisselsson, L., 1955. Electromyographic studies of the middle ear muscles of the cat. *EEG Clin. Neurophysiol.* 7, 399.

Galambos, R. und Rupert, A., 1959. Action of the middle ear muscles in normal cats. *J. Acoust. Soc. Amer.*, 31, 349.

Helmholtz, H. v., 1868. Die Mechanik der Gehörknöchelchen und des Trommelfelles. *Pflügers Arch. Ges. Physiol.*, 1, 1.

Hoffman, P., 1947. Über einen analysierbaren Fall der Begegnung von Erregungswellen im Zentralnervensystem. Nervenarzt *18*, 150.

Lindsay, J., Kobrak, H. und Perlman, H. B., 1936. Relations of the stapedius reflex to hearing sensation in man. *Arch. Otolaryng. (Chic.)*, 23, 671.

Lorente de Nó, R., 1935. The function of the central acoustic nuclei examined by means of the acoustic reflexes. *Laryngoscope* 45, 573.

Malmfors, T. und Wersäll, J., 1960. Innervation of the middle ear muscles in the rabbit with special reference to nerve calibres and motor units. *Acta Morph. Neerl. Scand.* 3, 163.

Ranke, O. F., 1953. Physiologie des Gehörs. In *Lehrbuch der Physiologie.* Springer, Berlin-Göttingen-Heidelberg.

Simmons, F. B., 1959. Middle ear muscle activity at moderate sound levels. *Ann. Otol.* 68, 1126.

Tsukamoto, H., Shinomiya, M. und Toida, M., 1936. Binnenohrmuskeln und Trommelfell. *Arch. Ohr. Nas. Kehlkopfheilk.*, 141, 185.

Wigand, M. E. und Bräter, St., 1964. Die Reflexaktivität motorischer Einheiten von Nervus und Musculus stapedius des wachen Kaninchens. 35. Jahresvers. Deutsch. Ges. HNO, Reichenhall 1964. *Arch. Ohr. Nas. Kehlkopfheilk.* (im Druck).

Wiggers, H. C., 1937. The functions of the intraaural muscles. *Amer. J. Physiol.* 120, 771.

Wullstein, H. L., 1958. Die Methode der Dekompression des Nervus facialis vom Austritt aus dem Labyrinth bis zu dem aus dem Foramen stylomastoideum ohne Beeinträchtigung des Mittelohres. *Arch. Ohr. Nas. Kehlkopfheilk.* 172, 582.

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Zeitverlauf der von einem Einzelimpuls angestoßenen Eigenschwingung am runden Fenster verfolgen. Er hat in den folgenden Bildern (Fig. 4 und 5) absichtlich eine relativ kleine Amplitude. Sie erkennen, daß vom Beginn bis zum Abklingen der von einem einzelnen Impuls angestoßenen Schwingung am runden Fenster mehr als 30 msec vergehen. (Darüber simultane Ableitungen vom Tensor tympani und aus der Halsmuskulatur in Zeilenschrift.) Die Erhöhung der Impuls-Folgefrequenz führt natürlich dazu, daß schließlich für ein vollständiges Ausschwingen die Zeit nicht mehr reicht. Die Schwingungen von rascher aufeinanderfolgenden Impulsen gehen zuletzt ineinander über. Hier, bei der Folgefrequenz 50/sec (Fig. 5), tritt jetzt erstmalig die Erscheinung auf, daß die Reflexaktivität im Stapediusmuskel so stark wird, daß seine Dämpfungswirkung den Ausschwingvorgang auf <20 msec verkürzt; und er wird so stark verkürzt, daß zwischen zwei aufeinanderfolgenden Eigenschwingungen die Nullinie wieder erreicht wird! Sie sehen es vielleicht noch besser auf dem nächsten Bild, auf dem die Zeitachse gedehnt wurde. Sie erkennen es dann auch bei der Folgefrequenz 100/sec.

Eine heuristische Betrachtung anzufügen, sei gestattet. Das Säugetier-Ohr ist wohl nicht vorgesehen zum Verarbeiten von Reintonreizen. Für eine den natürlichen Lebensbedingungen angepaßte Verarbeitung von akustischen Informationen ist viel wesentlicher, daß Ein- und Ausschwingvorgänge — kurz Transients — möglichst sauber getrennt wahrgenommen werden können. Und damit bin ich beim Ausgangspunkt, der hier zur Verhandlung stehenden Verbesserung der Informationsleitung des Gehörs, wieder angelangt. Der Stapediusreflex erhöht, ähnlich wie der Dämpfer auf der Klaviersaite, die Trennschärfe für Transients.

SUMMARY

Awake rabbits with high spinal section show middle ear muscle activity on low sound levels. Latency, firing rate, and fatigue of motor units are influenced by the stimulating tone frequency. The results of electrical stimulation of the stapedial nerve argue against the existence of proprioceptors in the stapedial muscle. The effect of middle ear muscle reflex on damping of oscillations, picked up at the round window, is demonstrated. It seems to be more important for the temporal reduction of transient oscillations than for decreasing their amplitudes.

RÉSUMÉ

Des lapins non anesthésiés à haute section cervicale montrent l'activité du muscule Stapédius sur stimuli d'intensité modérée. Les caractéristiques de latence, fréquence des réponses et fatigue des potentiels musculaires sont influencées par la fréquence du stimulus. Les résultats de la stimulation électrique du nerf stapédien mettent en doute l'existence de propriocepteurs dans le muscule stapédien.

Sénescence auriculaire

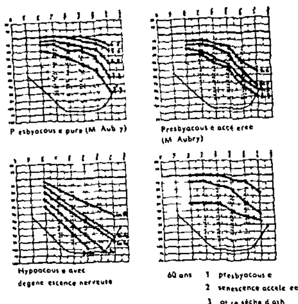


Fig. 1

Le *protocole d'examen* comportait d'abord un *examen otologique* avec interrogatoire et otoscopie. Le sujet subissait ensuite une *audiométrie tonale* oreilles séparées. Le *test d'intelligibilité* permettait la construction des courbes d'intelligibilité. *L'audiométrie phonétique cochléaire* explorait l'organe périphérique précisant le nombre de distorsions apparues à l'optimum de compréhension. Cet examen auditif vocal était complété par *l'étude de l'intégration auditive* biauriculaire grâce au test de Jean Claude Lafon. La *batterie des tests psychologiques* analysait la mémoire, l'attention, la structuration. Enfin une *enquête sociologique* permettait de replacer le vieillard dans le contexte de ses antécédents.

Nous avons établi au total les dossiers de 126 sujets de plus de 70 ans. Pour présenter les résultats des différents examens, nous les avons répartis en tranches de 5 ans. Parmi ces 126 sujets, on dénombre 106 femmes et 20 hommes. Le dépouillement s'est fait selon les méthodes mathématiques du calcul statistique.

A. *Épreuves audiométriques*

Les résultats de l'exploration tonale sont présentés sous la forme de courbes moyennes correspondant aux différentes tranches d'âge de 5 années.

Le simple examen des courbes permet de dire qu'elles sont extrêmement proches les unes des autres. Pour les fréquences conversationnelles et aiguës sur la population de 126 vieillards la diminution de l'intensité du seuil tonal n'est pas confirmée. Seules les fréquences graves 125, 250, 500 pré-

PREMIERS RÉSULTATS D'UNE ENQUÊTE MÉDICO-SOCIALE SUR L'AUDITION DU VIEILLARD[1]

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Travail de l'Institut d'Audio Phonologie de la Faculté de Médecine de Lyon (Dir. Prof. P. Mounier-Kuhn)

Les auteurs ont examiné 120 sujets de plus de 70 ans, vivant en communauté dans un hospice. Ils se sont attachés à une analyse de l'audition, au sens large du mot. Le protocole d'examen comportait un bilan otologique clinique, une audiométrie tonale, des épreuves audiométriques vocales avec test d'intelligibilité et test phonétique cochléaire, des épreuves psychologiques. Les résultats ont été dépouillés selon des méthodes statistiques. Ils comparent les résultats des différents examens entre eux, puis ils confrontent les courbes tonales moyennes à celles de 120 sujets âgés de plus de 70 ans examinés à une consultation hospitalière d'audiologie.

Nous avons entrepris une enquête sur l'audition du vieillard pour vérifier un certain nombre de notions classiques admises à propos de la presbyacousie et pour situer la place de la sénescence auriculaire dans l'ensemble de la sénescence psycho-physiologique.

Les descriptions classiques de la presbyacousie distinguent *trois grandes formes audiométriques*:

— *la presbyacousie pure*: la perte tonale est minime jusqu'à 70 ans. Il faut attendre 80 ou 90 ans pour qu'une gêne sociale se manifeste de façon importante.

— *la presbyacousie accélérée* offre un tableau identique. Elle se différencie de la précédente au point de vue tonal, par le décalage de 15 à 20 ans sur les courbes.

— *la surdité par dégénérescence nerveuse* se caractérise par des courbes à pente beaucoup plus accentuée. C'est, en fait, lors des épreuves vocales que se révèle la discordance, très nette, entre celles-ci et la courbe tonale.

Nous avons examiné les vieillards âgés de plus de 70 ans vivant dans la communauté d'un Hospice. Ce choix fut motivé par un désir d'homogénéité de la population explorée. Le groupement facilitait, sur le plan matériel, la pratique des tests.

[1] Cette enquête a été entreprise — et sera poursuivie — grâce à une subvention de la Caisse Régionale de Sécurité Sociale « Rhône-Alpes ».

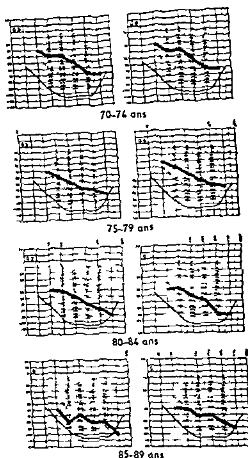


Fig. 3

Les résultats avec *le test phonétique cochléaire* sont superposables à ceux du test d'intelligibilité.

Nous avons accordé une place à part, dans notre examen, au test de J. C. Lafon. Ce test nous offre la possibilité d'étudier *la fonction d'intégration auditive*.

Sur 119 sujets examinés avec ce test, 24, soit 20 %, étaient porteurs d'un trouble d'intégration. Cette *recherche est non seulement intéressante* lorsqu'elle est comparée aux autres épreuves, mais aussi à titre thérapeutique : l'existence *d'un trouble d'intégration contre-indique formellement le port* d'un appareil prothétique ; toute tentative est vouée à un échec certain.

Le graphique représente *la répartition des cas en deux groupes*, avec ou sans troubles d'intégration. La diagonale est la ligne de l'écart normal théorique. La droite *qui coupe* l'axe des abscisses au point 3 marque la limite entre la ligne théorique et les cas pathologiques. Dans cette dernière éventualité, la *différence* entre le nombre d'erreurs phonémiques sans et avec bruit est significative.

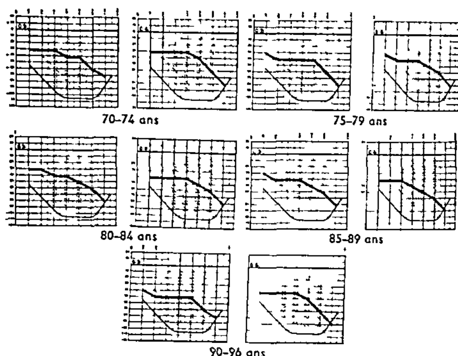


Fig. 2

sentent une baisse régulière avec l'âge. Dans ces cas, la surdité ne dépend pas de l'âge mais de l'individu.

Il nous a paru intéressant de comparer les données de ces examens avec ceux de sujets âgés de plus de 70 ans venus à la consultation d'otologie de la clinique O.R.L. Nous avons utilisé le même mode de dépouillement et nous présentons les résultats sous la forme de courbes moyennes par tranches de 5 ans.

L'analyse des courbes selon les tranches d'âge montre une baisse tonale progressive du seuil tonal sur toutes les fréquences. Mais cette population était hétérogène, comprenant des sujets porteurs d'affections pathologiques de l'oreille.

La comparaison entre les deux groupes de vieillards permet de les opposer sur le plan du vieillissement otologique. Dans l'un et l'autre cas, la perte tonale sur les fréquences graves est plus importante que ne l'affirment les données classiques.

Les épreuves vocales étaient au nombre de trois : test d'intelligibilité, test phonétique cochléaire et test phonétique d'intégration.

Pour chaque tranche d'âge de 5 ans, nous avons calculé pour trois intensités le nombre moyen des distorsions lorsqu'on utilise *les listes du test d'intelligibilité*. Les courbes moyennes d'intelligibilité reproduites ici marquent l'impossibilité statistique d'obtenir 100 % d'intelligibilité chez le vieillard.

Au fur et à mesure que l'âge avance, la courbe dessine un dôme dont la pente terminale est de plus en plus marquée. En réalité, dans 65 cas sur 123, le 100 % d'intelligibilité fut obtenu, soit dans la moitié des cas.

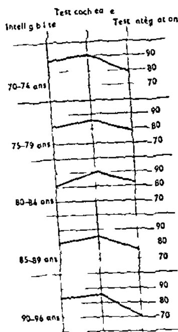
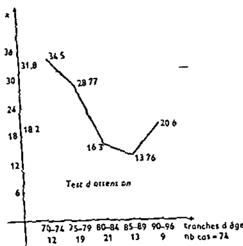


FIG 6



FIG

régression phonémique du vieillard La compréhension du vieillard est meilleure pour la phrase que pour le mot pour le mot que pour le phonème

B Épreuves psychologiques

Trois tests psychologiques nous ont permis par un examen qui n était pas trop long et qui intéressait le sujet de cerner quelques fonctions essentielles sinon para auditives, tout au moins intervenant dans l élaboration conceptuelle du langage

L étude de l attention utilisa le test des deux barrages de Zazzo Nous avons été surpris de constater que les sujets ont bien fixé leur attention sur *un test de 10 minutes alors que nous nous attendions à une certaine* fatigue de l attention Le vieillard est capable de faire une tâche assez longtemps mais l adaptation est longue Une fois adapté il peut fixer son attention la tâche doit être simple

Les résultats sont présentés sous la *forme* d une courbe Elle indique parfaitement le déclin progressif de l attention, mais les vieillards qui ont franchi le cap de 90 ans paraissent conserver une fonction meilleure que ne le ferait supposer une courbe de décroissance parallèle à celle de l âge

Pour *l étude de la structuration* l épreuve choisie fut l item « arrangement d images » de la batterie adulte du Weschler (échelle de performance) Ce test mesure effectivement l aptitude du sujet à comprendre et à saisir une situation dans son ensemble

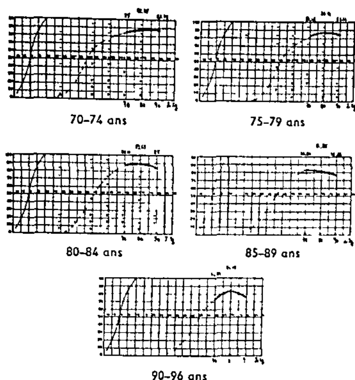


FIG 4

Si l'on juxtapose les résultats des trois tests d'intelligibilité, cochléaire et d'intégration à 90 db et par tranche d'âge de 5 ans, les résultats du test d'intelligibilité et du test cochléaire apparaissent superposables. Le test d'intégration fait apparaître beaucoup plus de distorsions, ce qui vérifie la

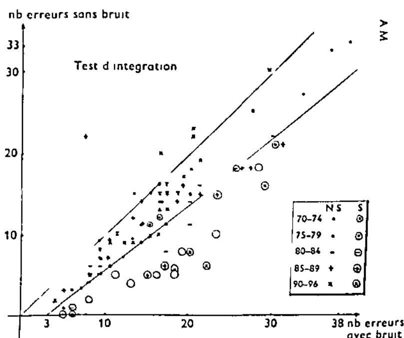


FIG 5 Répartition des cas en deux groupes avec ou sans trouble d'intégration. La diagonale est la ligne de l'écart normal

SUMMARY

120 Subjects, over 70 years old, living together in an hospice, have been examined. The hearing, in most of the aspects, was the purpose of the research. All subjects were given a test battery consisting of *otological clinical examination*, pure tone audiogram, air and bone conduction, vocal tests including intelligibility test, phonetic cochlear discrimination test, and psychological evaluation. The results have been statistically evaluated and compared. In the results of the tonal test, the average thresholds were taken, and compared with those of an other group of 120 veterans, over 70 years old, clinically examined in a hearing Center.

ZUSAMMENFASSUNG

Die Verfasser haben 120 Greise von über 70 Jahren untersucht, die in der Gemeinschaft eines Altersheimes lebten, und sich besonders mit einer Analyse der Hörfähigkeit im weitesten Sinne des Wortes befasst. Das Protokoll der Untersuchung enthält eine klinisch otologische Bilanz, ton- und sprachaudiometrische Prüfungen mit Verständlichkeitstest, phonetischem Test der Schnecke und schliesslich psychologische *Prüfungen*. Die Ergebnisse sind nach statistischen Methoden verarbeitet worden. Sie vergleichen die Ergebnisse der verschiedenen Untersuchungen untereinander. Dann wurden die mittleren Tonschwellenkurven mit denen von 120 Greisen im Alter von über 70 Jahren, die in einer audiologischen Krankenhaussprechstunde untersucht wurden, verglichen.

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DISCUSSION

J. M. Tato: Nous sommes en train d'étudier la presbyacousie chez des races autonomes de l'Amérique latine, surtout du Pérou. Nous n'avons pas fini la recherche qui doit comprendre 10 000 personnes, pour atteindre la signification essentielle et le résultat statistique n'est pas encore fait, mais nous pouvons dire que les chiffres sont beaucoup meilleurs que les donnés par des recherches américaines dans l'Amérique du Nord (U.S.A.) et pires que ceux donnés par Rosen sur les Soudanais en Afrique. Il faut dire que les Indiens des plateaux et montagnes souffrent très peu de l'appareil vasculaire et la nutrition est pauvre de protéines animales.

P. Mounier-Kuhn (Réponse): Je remercie le *Professeur Tato* de son intéressante contribution aux recherches que je poursuis sur l'état auditif du vieillard. Ce qui est important pour moi, est de mettre en évidence toutes les possibilités d'ordre thérapeutique, afin d'atténuer l'isolement du vieillard.

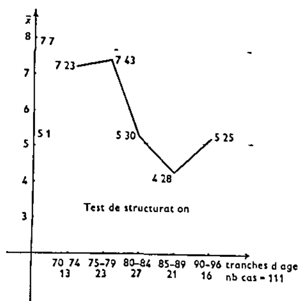


Fig 8

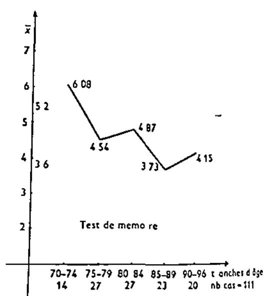


Fig 9

La capacité d'appréhension globale est, chez le vieillard, très atteinte La courbe construite pour illustrer les résultats est en tout point superposable à celle de l'attention

L'épreuve choisie pour *l'étude de la mémoire* est la liste de mots de Rey qui teste la mémoire immédiate Le vieillard n'a plus de possibilités de mémorisation, c'est l'une des raisons pour laquelle il est dysstructuré Cette épreuve exacerbait, chez les sujets examinés, la conscience aiguë qu'ils avaient de leur difficulté de mémorisation

Le graphique marque bien la décroissance progressive avec cette remontée que nous avons retrouvée, lors des trois tests psychologiques

Le point critique pour attention et structuration est 80 ans, alors que pour la mémoire il est à 74 ans, marquant ainsi le vieillissement plus précoce de la mémoire

CONCLUSIONS GÉNÉRALES

Notre enquête a porté sur 126 vieillards d'un hospice, formant un groupe homogène L'état auditif du vieillard dépend moins de l'âge que du vieillissement général de l'organisme Cette affirmation doit être nuancée par une autre notion, celle de l'atteinte parfois plus précoce de l'appareil auditif par rapport à d'autres appareils

Cette enquête sur l'audition du vieillard peut autoriser une attitude thérapeutique positive Dans 46 cas sur 126, les examens audiométriques tonaux et vocaux permettaient de laisser présager de l'excellence du résultat prothétique L'appareillage n'est, certes, qu'une solution palliative, mais il est un premier pas vers le reclassement de sujets que tout tend à fermer sur eux-mêmes

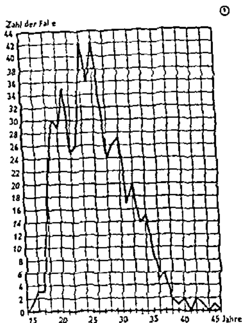


Abb. 1. Alterskurve der Fruchtbarkeit bei der Frau (500 Fälle)

wicklung der Otosklerose vorangehenden für Entstehung dieser Krankheit negativ.

Die Abhängigkeit der Entwicklung der Otosklerose von der Schwangerschaft wurde danach beurteilt, dass diese Erkrankung entweder im Laufe der Gravidität oder nach deren Abschluss, *spätestens jedoch innerhalb von* 6 Monaten manifest wurde.

Diese Grenze der Abhängigkeit oder Unabhängigkeit der Entwicklung der Otosklerose von der Schwangerschaft wurde von Barton übernommen. In Übereinstimmung mit diesem Verfasser wird dieselbe jedoch nur als approximativ und vorläufig angesehen. In der ganzen Reihe der untersuchten, an Otosklerose leidenden Frauen bewegte sich das Schwangerschaftsalter zwischen 15 und 45 Jahren.

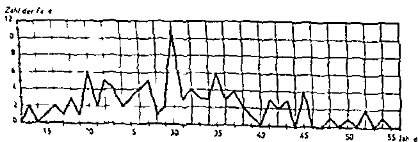


Abb. 2. Altersvorkommen von 100 Otosklerosefällen bei Frauen

DIE ONTOGENETISCHE BEZIEHUNG DER SCHWANGERSCHAFT ZUR ENTSTEHUNG UND ENTWICKLUNG DER OTOSKLEROSE

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Die genaue Analyse des eigenen Materials ergab, dass in den bekannten Beziehungen zwischen der Otosklerose und der Schwangerschaft gewisse Gesetzmässigkeiten in der Ontogenese existieren, die genauer geklärt werden.

Im Laufe der bisherigen Otoskleroseforschung stellten wir fest, dass diese Erkrankung in einer gewissen Beziehung zur relativen Fruchtbarkeitskurve steht, die eine charakteristische und konstante Form aufweist (Abb 1) Diese Kurve beginnt bei Frauen im Alter von 15 Jahren und endet bei 45 Jahren. Die Kurve weist drei Abschnitte auf: den aufsteigenden Abschnitt (von 15 bis zu 19 Jahren), den Gipfelabschnitt (von 19–21 bis zu 29–30 Jahren) und einen absteigenden Abschnitt (von 29–30 Jahren bis zu einem Alter von 43–45 Jahren).

Diese Kurve wurde in einer früheren Arbeit mit den Kurven des zeitlichen Vorkommens einer Serie von 100 Fällen von Otosklerose korreliert Es wurde dabei die Beziehung der Fruchtbarkeitskurve zum zeitlichen Vorkommen der *Otosklerose in beiden Geschlechtern zusammen* sowie bei jedem Geschlecht getrennt gewertet (Přecechtěl, 1963 und 1964)

In der vorliegenden Mitteilung wurde eine Reihengruppe von 100 Fällen von Otosklerose bei Frauen bearbeitet, um die Beziehung der Schwangerschaft zum Beginn der Otoskleroseentwicklung zu untersuchen Ihr Altersvorkommen ist in dem Diagramm (Abb 2) festgehalten

Es wurde festgestellt, dass die ersten Symptome der Otosklerose frühestens im 13 Lebensjahre und spätestens im Alter von 54 Jahren vorkamen Das Maximum der Entstehung der Otosklerose war im Alter von 30 Jahren

Anhand unseres Materials konnte eine Altersbeziehung der Schwangerschaft zur Otosklerose in 75 Fällen in der folgenden Verteilung festgestellt werden

1 in 19 Fällen wurde eine positive Beziehung der Schwangerschaft zum Beginn der Otosklerose ermittelt,

2 in 56 Fällen bestand keine Beziehung der Gravidität zur Entwicklung der Otosklerose

Davon a) entstand die Otosklerose in 18 Fällen vor der ersten Schwangerschaft, b) in 38 Fällen war die Bedeutung der Schwangerschaft, der Ent-

wurden Die Anzahl dieser Falle war 18 Diese Untergruppe beginnt bereits in der Kindheit und endet im Alter von 36 Jahren Die meisten dieser Falle (insgesamt 11) kamen im Alter von 15–22 Jahren vor

In dieser Untergruppe der Otosklerosen befanden sich zwei Falle bei denen sich das Gehor im Laufe der Schwangerschaft verbesserte

In einem Falle (Jandova I Nr 366/1957) begann die Entwicklung der Otoskle [illegible] Laufe der ersten Schwangerschaft im Alter [illegible]

Zweiter Fall Svarcova R (ambul Nr *6140/1960*) *begann* [illegible] Alter von 18 Jahren (1939) Drei Geburten im Jahre 1944 1948 1956 Im Laufe der drei Schwangerschaften verbesserte sich das Gehor (betrachtliche Besserung des Horvermogens fur die Konversationssprache) Nach Schwangerschaftsende verschlechterte sich der Zustand des Gehors bis zu dem ursprunglichen Horvermogen Diese Frau wies *im Laufe* der Schwangerschaft einen auffallenden Gewichtsanstieg auf (um 11 13 und 12 kg) Das Gewicht der Kinder bei der Geburt war in kg 2 80 4 00 3 30

Die zweite Untergruppe der Otosklerosen von der Schwangerschaft unabhangig kann aus den Fallen gebildet werden bei denen sich die Erkrankung im Laufe der zwischen zwei Schwangerschaften gelegenen Zeitspanne entwickelte (in verschiedenen Altersintervallen je nach Anzahl der Schwangerschaften und in genugendem *Zeitabstand* der mehr als 6 Monate nach der letzten Schwangerschaft vor Beginn der Otosklerose betrug) Die Anzahl dieser Falle war 7 ihre Altersverteilung lag zwischen 28 und 41 Jahren Eine zusammenhangende Gruppe von 5 Fallen lag in den Altersgrenzen von 28 bis 31 Jahren das Maximum war bei 30 Jahren — 2 Falle die ubrigen 2 Falle *waren einzeln im Alter von 35 und 41 Jahren*

Die dritte Untergruppe der Unabhangigkeit der Otosklerose von der Schwangerschaft stellen diejenigen Fallen vor, die sich erst nach der letzten Schwangerschaft entwickelten und innerhalb eines langeren Zeitintervalles als 6 Monate nach Schwangerschaftsabschluss entstanden Die Anzahl dieser Falle war 31 *Das Maximum in dieser* Gruppe liegt bei 30 Jahren (5 Fall

Durch die Verbindung der Falle der zweiten und dritten Untergruppe entstand eine Gruppe von 38 Fallen aus denen eine Alterskurve der entwicklungsgemass schwangerschaftsunabhangigen Otosklerosen (Abb 4) gebildet wurde Der Altersbereich dieser Kurve betragt 24 54 Jahre

Die folgenden Beziehungen dieser Kurve konnen beobachtet werden a) diejenigen zur Fruchtbarkeitskurve b) zur Kurve der 100 Falle unserer Otosklerosenreihe und c) zur Abhangigkeitskurve der Otosk*lerosenent*wicklung von der Schwangerschaft

ad a Die Unabhangigkeitskurve der zweiten und dritten Untergruppe und die Fruchtbarkeitskurve weisen den gleichen zeitlichen Bereich von 30 Jahren auf zwischen beiden Kurven besteht jedoch eine Altersverschiebung



Abb. 3. Alterskurve der Otosklerose in Abhängigkeit von der Schwangerschaft

A. *Gruppe der Abhängigkeit der Entstehung der Otosklerose von der Schwangerschaft* (19 Fälle)

Die Entstehung der Otosklerose in Abhängigkeit von der Schwangerschaft (weiter nur Abhängigkeitsgruppe) wurde entweder im Laufe derselben (5 Fälle) oder nach Ablauf der Schwangerschaft, spätestens innerhalb von 6 Monaten (14 Fälle), beobachtet. Beide Gruppen (19 Fälle) wurden in einer Kurve für entwicklungsgemäss schwangerschaftsabhängige Otosklerosefälle vereint (Abb. 3). Diese Fälle wurden in einem Lebensalter von 21 bis 34 Jahren ermittelt. Das Maximum der Fälle ist gleich am Anfang der Kurve.

Vergleicht man nun diese Kurve mit der Fruchtbarkeitskurve, so wird es klar, dass der Beginn der Abhängigkeitskurve mit dem Beginn des Gipfelabschnittes der Fruchtbarkeitskurve übereinstimmt und bis in den oberen Abschnitt ihres absteigenden Teiles hineinreicht. Daraus kann darauf geurteilt werden, dass zur Aktivierung der Otosklerose durch die Schwangerschaft bei disponierten Frauen eine gewisse vitale Potenz notwendig ist, welche auch in deren Fertilität zur Geltung kommt.

Die Abhängigkeitskurve liegt zwar ebenfalls in den Altersgrenzen des maximalen Vorkommens der Otosklerose (Alter von 30 Jahren), zugleich geht jedoch daraus hervor, dass sich in diesem Lebensalter die Schwangerschaft bei der Aktivierung der Otosklerosebasis nicht geltend macht, die Abhängigkeitskurve weist für das Alter von 30 Jahren eine tiefe Depression auf. Daraus geht hervor, dass der die Otosklerose in diesem Lebensalter aktivierende Faktor wahrscheinlich einen anderen Charakter besitzt als derjenige, der über die Schwangerschaft hin mit der Otosklerose in Beziehung steht.

In dieser Abhängigkeitsgruppe kam in 10 von 19 Fällen noch eine weitere Schwangerschaft vor. Bei 5 derselben kam wieder eine Abhängigkeit der Otosklerose von der Gravidität zur Geltung (50%), bei 5 weiteren jedoch nicht (50%).

B. *Gruppe der Unabhängigkeit der Entstehung der Otosklerose von der Schwangerschaft* (38 Fälle)

Die Gruppe der Otosklerosen, deren Entstehung von der Schwangerschaft unabhängig war, kann in drei Untergruppen eingeteilt werden.

Die erstere derselben bilden diejenigen Fälle, bei denen die ersten Symptome der Erkrankung bereits vor der ersten Schwangerschaft beobachtet

die Schwangerschaft im verschiedenen Alter keine einheitliche Wirkung auf die Entstehung und die Entwicklung der Otosklerose ausübt

In unserem Material befindet sich sogar ein Fall (Skodová, V., Krankheitsbeschreibung Nr. *234/1959*), in dem sich bei preventiver Schwangerschaftsunterbrechung anhand einer anderen Indikation, als Otosklerose (Rubeolla), innerhalb von einem Monat nach dem Eingriff bei einer 21jährigen, bis dahin gesunden Frau Otosklerose entwickelte. Ihre Mutter war schwerhörig und wahrscheinlich an Otosklerose leidend

SUMMARY

The influence of pregnancy on the onset of otosclerosis was studied in *100* females. Only 75 cases could be evaluated from the registrations. In 18 women otosclerosis began before the first pregnancy, in 19 of them the influence of pregnancy on the beginning of otosclerosis was positive, in 38 women negative.

In existing otosclerosis the positive influence of pregnancy appeared generally by deterioration, only exceptionally by transient improvement of the state (2 cases).

From this paper it is possible to conclude (1) that the pathogenesis of otosclerosis is dependent on pregnancy in different ways, especially in ontogenesis, (2) that on the basis of this paper a further adequate precization of the indication to artificial abortion because of otosclerosis can be attained

RÉSUMÉ

L'analyse en détail du matériel propre a montré qu'ils existent dans les relations connues entre l'otosclérose et la grossesse, certains régularités dans l'ontogenèse qui seront expliquées

LITERATUR

Ashcroft, D. W., 1935 Two cases of otosclerosis paradoxica. *J. Laryng.*, *50* 268–270

Barton, R. T., 1945 *The influence of pregnancy on otosclerosis. New Engl. J. Med.* 233 433

Přecechtěl, A., 1963 Věkové zákonitosti v plodnosti žen a jejich vztah k vývoji otosklerózy. *Čes. Otolaryng.* 12 6

1964 Age regularities in the fertility of women and their relation to the development of otosclerosis. *Acta Otolaryng. (Stockh.)* 57

1964 Ontogenetický vztah těhotenství k začátku vývoje otosklerózy. *Čes. Otolaryng.* XIII

17 Karmelitská Praha III Tschechoslowakei



Abb. 4. Alterskurve der von der Schwangerschaft unabhängigen Otosklerose

Die Fruchtbarkeitskurve beginnt im Alter von 15 Jahren und endet bei 45 Jahren. Die Unabhängigkeitskurve beginnt erst im Alter von 24 und endet in demjenigen von 54 Jahren.

ad b) Sowohl die Unabhängigkeitskurve als auch diejenige der Gesamtanzahl aller Otosklerosefälle (100) besitzt ein Maximum bei dem Alter von 30 Jahren.

ad c) Im Diagramm (Abb. 5) sind beide Kurven, diejenige der Abhängigkeit sowie diejenige der *Unabhängigkeit*, dargestellt. Aus dem Vergleich beider geht hervor, dass:

1. der zeitliche Bereich der Abhängigkeitskurve um mehr als die Hälfte kürzer ist (13 Jahre) als dasjenige der Unabhängigkeitskurve (30 Jahre);
2. das zahlenmässige Verhältnis beider Gruppen 19 : 38 (1 . 2) beträgt. Dieses Verhältnis ist wahrscheinlich nicht nur durch den zeitlichen Bereich bedingt, sondern auch durch andere Faktoren der Ontogenese
3. der Beginn der Abhängigkeitskurve — gegen denjenigen der Unabhängigkeitskurve — in einen niedrigeren Alterbereich verschoben ist
4. in dem Altersabschnitte von 28–32 Jahren, in dem die Anzahl der Otosklerosen am grössten ist, beide Kurven eine entgegengesetzte Ausschwingung aufweisen (Maximum der Unabhängigkeitsfälle, Minimum der Abhängigkeitsfälle)
5. die Abhängigkeitsgruppe ihr Maximum an den Beginn des Gipfelabschnittes der Fruchtbarkeitskurve (Alter von 22 Jahren) projiziert Die Unabhängigkeitskurve beginnt erst im Alter von 24 Jahren mit zwei Gipfeln im Alter von 26 und 30 Jahren, meistens liegt dieselbe jedoch im Alter verminderter Fertilität und endet erst im Klimakterium

Aus allen oben angeführten Beziehungen kann darauf geurteilt werden, dass die Pathogenese der Otosklerose nicht einheitlich ist und dass auch

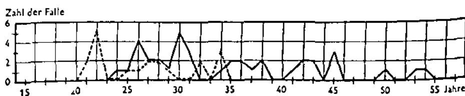


Abb. 5. Gegenüberstellung der Kurven 3 und 4

einigermassen federn kann wenn aber die Stapesplatte in einem grosseren Bereich ihres Umfanges fixiert ist wird der Stapes *immobil* *In diesem Moment* musste also die Leitungsschwerhorigkeit schon den hochsten Grad erreicht haben Weitere Fixation der Stapesplatte an dem Rand des ovalen Fensters *konnte also keinen* weiteren Einfluss auf den Grad der Leitungs schwerhorigkeit ausuben Und wenn wir auch voraussetzen dass die Verknocherung des anularen Ligaments sehr langsam fortschreitet *kann man* doch nicht annehmen dass dieser Prozess in einem Teil seines Umfanges jahrelang dauert da sich in dieser Hinsicht der Knochen des Labyrinthes *nicht anders als jeder* andere Knochen im Korper benehmen kann

Wir mussen deshalb annehmen dass fur die Progressivitat der Leitungs schwerhorigkeit noch ein anderer Faktor, der der Stapesfixation voraus geht verantwortlich ist und dass zur Zeit der Fixation der Stapesplatte an einem grosseren Teil des Umfanges des ovalen Fensters der maximale *Grad der* Leitungsschwerhorigkeit erreicht ist

Holmgren und Sourdille haben schon auf die Moglichkeit einer Dekompression der Labyrinthflussigkeit bei der Otosklerose durch Fenestration hingewiesen Wittmaack spricht von einem Hydrops labyrinthi bei der Otosklerose

M Meyer (1939) berichtet uber Besserungen der Leitungs ja sogar der Innenohrschwerhorigkeit bei 21 Otosklerosen sowie bei 5 labyrintharen Hypoakusien *durch subokzipitale Punktion Dabei verschwanden auch die* Gerausche Er schloss daraus dass bei Otosklerose nicht die Stapesfixation allein fur die Leitungsschwerhorigkeit verantwortlich sein kann sondern dass daran auch der erhohte labyrinthare Druck beteiligt ist

Georges und Michel Portmann (1951) haben auf einen sekundaren oder primaren Hydrops des Labyrinthes bei der Otosklerose aufmerksam gemacht und eine Dekompression durch Fenestration oder Diszision des *Saccus endolymphaticus (G Portmann)* vorgeschlagen

Es wird also von mehreren Autoren auf eine Druckerhohung im Labyrinth bei der Otosklerose hingewiesen Und gerade diese Druckerhohung ist unserer Meinung nach fur die Progressivitat der Leitungsschwerhorigkeit die nicht durch den Grad der Stapesfixation erklart werden kann verantwortlich

Ranke (1[illegible]3) hat wie bekannt die beiden Aquadukte und samtliche *perineuralen* und perivascularen Kanale der knochernen Labyrinthkapsel als das 3 Schneckenfenster bezeichnet Tonndorf konnte im Tierversuch feststellen dass in ahnlicher Form wie das ovale Fenster mit Hinblick auf die Knochenleitung den funktionellen Opponenten des runden Fensters darstellt so kann auch der Aquaeductus vestibuli als der funktionelle Opponent des Aquaeductus *cochleae angesehen werden*

Wir glauben dass die Serzersche anthropologische Theorie der Atiopathogenese der Otosklerose diejenige ist die uns das Zustandekommen dieser Druckerhohung erklaren kann Wenn es durch Schadelbasiskyphose zur Kompression des Labyrinthkerns und der knochernen Kanale in der Pyra

EIN ERKLÄRUNGSVERSUCH ZUR PROGRESSIVITÄT DER LEITUNGS-SCHWERHÖRIGKEIT BEI DER OTOSKLEROSE

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Die langjährige Progressivität der Schalleitungsschwerhörigkeit kann bei der Otosklerose nicht allein durch den Grad der Stapesfixation geklärt werden, da schon bei der Fixation des Stapes nur entlang einem grösseren Teil seines Umfanges seine Beweglichkeit verlorengeht. Unserer Meinung nach handelt es sich hier um einen chronischen Hydrops des Labyrinthes, der durch die Kompression des Aquaeductus cochleae bzw. der gleichnamigen Vene als Folge der Schädelbasiskyphose zustande kommt.

Durch die Arbeiten von Prof. Ruedi (1961, 1962) angeregt, haben wir uns entschlossen, unsere Ansicht über die Ätiopathogenese, Symptomatologie und Therapie der Otosklerose vorzubringen. Die statistischen Data von Ruedi, die für die Fenestration in der Therapie der Otosklerose und gegen die Mobilisation und Interposition sprechen, haben uns besonders dazu veranlasst. Das ist übrigens die Idee, die Sourdille, der grosse Meister auf dem Gebiet der Otosklerose, sein ganzes Leben lang gegen einen grossen Widerstand besonders der amerikanischen Autoren propagiert und verteidigt hat.

Wenn man von der Symptomatologie der Otosklerose spricht, sagt man, dass sie durch progressive konduktive Schwerhörigkeit, die vom Grad der Stapesfixation bzw. dem Umfang der Obturation des runden Fensters abhängt, charakterisiert ist. Diese Leitungsschwerhörigkeit wird später von einer Innenohrschwerhörigkeit, die zum völligen Hörverlust führt, begleitet.

Soweit es sich um eine Obturation des runden Fensters handelt, können wir uns leicht vorstellen, dass die Osteophyten das runde Fenster langsam verengen, bis es schliesslich komplett verlegt wird, was sich mit einer progressiven Leitungsschwerhörigkeit manifestiert. Wenn aber der Prozess im Bereiche des ovalen Fensters lokalisiert ist, kann der Grad der Leitungsschwerhörigkeit keinesfalls vom Grad der Stapesfixation abhängen, da zur Zeit, wo der Stapes fixiert ist, er seine Bewegungsfähigkeit verliert. Wenn nur wenige Brücken zwischen dem Rand des ovalen Fensters und der Stapesplatte gebildet sind, können wir noch annehmen, dass die Stapesplatte

einigermassen federn kann wenn aber die Stapesplatte in einem grösseren Bereich ihres Umfanges fixiert ist wird der Stapes immobil In diesem Moment müsste also die Leitungsschwerhörigkeit schon den höchsten Grad erreicht haben Weitere Fixation der Stapesplatte an dem Rand des ovalen Fensters könnte also keinen weiteren Einfluss auf den Grad der Leitungsschwerhörigkeit ausüben Und wenn wir auch voraussetzen dass die Verknöcherung des anulären Ligaments sehr langsam fortschreitet kann man doch nicht annehmen dass dieser Prozess in einem Teil seines Umfanges jahrelang dauert da sich in dieser Hinsicht der Knochen des Labyrinthes nicht anders als jeder andere Knochen im Körper benehmen kann

Wir müssen deshalb annehmen dass für die Progressivität der Leitungsschwerhörigkeit noch ein anderer Faktor, der der Stapesfixation voraus geht, verantwortlich ist und dass zur Zeit der Fixation der Stapesplatte an einem grösseren Teil des Umfanges des ovalen Fensters der maximale Grad der Leitungsschwerhörigkeit erreicht ist

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Abb. 1.



Abb. 2.

Abb. 1. Apertura externa canaliculi cochleae und Apertura Venae canaliculi cochleae bei einem Embryo von 253 mm Sch. St. L.
Abb. 2. Apertura externa canaliculi cochleae und die Austrittstelle der Vena canaliculi cochleae bei einem 386 mm langen Fötus.

rinde, durch welche die Arterien und Venen zur Labyrinthkapsel hindurchtreten, kommt, müssen wir annehmen, dass dadurch auch der Aquaeductus cochleae bzw. der parallel verlaufende Kanal für die V. canaliculi cochleae komprimiert sein wird. Die Kompression der kochlearen Vene, die die Hauptmenge des venösen Blutes aus dem membranösen Labyrinth drainiert, wird zu einer Venostase führen, ebenso wie die Kompression des cochlearen Kanälchens zu einem erschwerten Austausch zwischen der Labyrinthflüssigkeit und dem Liquor führen muss. Die Venostase, die sich durch eine lange Zeitperiode hindurch entwickelt, wird ihrerseits zu einer Störung in der Produktion der Perilymphe, die nach Graf & Poretti (1950) sowie Naftalin & Harrison (1958) durch Ultrafiltration aus dem Blut entsteht, führen. Es wird dadurch notwendig zu einem chronischen Hydrops des Labyrinthes durch eine lange Zeitperiode kommen und dies scheint uns derjenige Faktor zu sein, der für eine Progressivität der Leitungsschwerhörigkeit verantwortlich ist.

Der Aquaeductus cochleae wurde von mehreren Autoren auf seinen Bau und seine Durchgängigkeit beim Kaninchen und Menschen histologisch und experimentell untersucht (Y. Meurman, 1930, Streeter, Karlefors, u. a.).

Winckler (1963) hat den Aquaeductus cochleae bei der Katze, beim Lamm, beim Ochsen und bei menschlichen Föten sowie an erwachsenen Menschen eingehend studiert. Während bei den genannten Säugetieren und beim menschlichen Fötus der Kanal sondierbar ist, kann man ihn beim erwachsenen Menschen schwer sondieren, so dass man ihn mit der Fräse darstellen muss. Er äussert die Meinung, dass der Aquaeductus cochleae beim erwachsenen Menschen so eng ist, um von den Druckschwankungen des Liquors die Perilymphe zu schützen. Delattre hat in der Diskussion richtig bemerkt, dass der abgebogene Verlauf des Canaliculus cochleae beim

Erwachsenen, den Winckler beschreibt, mit der Rotation der Pyramide in Zusammenhang steht. Meurman hat gefunden, dass der Canaliculus cochleae bei Menschen cca 10 mm lang ist und einen Arachnoidealstrang der im engsten Teil des Kanals meist fest ist, enthält Im Anfang und an der Einmündung ist das Bindegewebe locker. Selten kann es durch Endostwucherung zur Obliteration des Kanals in seinem engsten *Abschnitt kommen* Es besteht nach Meurman die Möglichkeit, dass der Kanal erst nach dem 50 Jahr verengt wird Das Arachnoidealgewebe steht mit der Arachnoidea um den N glossopharyngeus *in Zusammenhang.*

Der Arachnoidealstrang enthält wenige Gefässe. Die Vena aquaeductus cochleae geht durch einen eigenen Kanal, der in der Scala tympani breiter *und an* der Basis der Pyramide enger als die entsprechende Öffnung des *Aquaeductus cochleae* ist. Der engste Abschnitt der beiden ist ungefähr gleich breit Young (1952) hat neulichst an Abgüssen *vom Schlafenbein* feststellen können, dass der Canaliculus cochleae ebenso wie der Canaliculus vestibuli eine sackförmige Erweiterung, die an seinem Ende liegt, *bildet*

Es muss bei der erwähnten Kompression des Aquaeductus bzw der Vene nicht zu menièreförmigen Symptomen kommen, da der Hydrops sehr langsam zustande kommt, ähnlich wie sich auch ein chronischer Hydrocephalus langsam ohne alarmante Symptome entwickelt

Einige Tatsachen sprechen für unsere Ansicht Wenn wir die Öffnung des Aquaeductus cochleae und diejenige für die Vene an der unteren Seite der Pyramide betrachten, sehen wir, dass die beiden in manchen Fällen sehr verengt sind, ähnlich wie dies Šercer für den Canaliculus tympanicus feststellen konnte

Einen Beweis, dass es zur Kompression der Kanäle in der Pyramide kommt, haben uns diejenigen Fälle geliefert, wo die Patienten, bei denen die Otosklerose operativ verifiziert war, über einen langdauernden salzigen Geschmack klagten In diesen Fällen handelt es sich sicher um *eine Irritation* der Chorda tympani wahrscheinlich an der Stelle, wo sie durch den gleichnamigen Kanal zusammen mit der Arteria tympanica posterior hindurchtritt Dass es zu einer Deformation und Dislokation der Kanäle in der Pyramide kommen kann, haben wir mit unseren Beobachtungen bei platybasischen Schädeln bewiesen Wir haben festgestellt, dass es *durch Kompression* nicht nur zu einer Deformation des Labyrinthes, sondern auch zu einer Dislokation des facialen Kanals gekommen ist

Noch eine weitere Beobachtung spricht für unsere Auffassung Man findet manchesmal bei jungen Leuten mit dem klinischen Bild einer Otosklerose bei der Operation weder die Stapesfixation *noch die Obturation* der Fenestra rotunda und doch führt bei ihnen eine Fenestration zur Besserung des *Zustandes*

Anderseits führt bei einigen älteren Patienten in Fällen von Otosklerose, wo der Stapes durch Osteophyten fixiert ist, die Fenestration nicht zum gewünschten Erfolg Man muss annehmen, dass *in diesen Fällen die* Otoskle-



Abb. 1



Abb. 2

Abb. 1. Apertura externa canaliculi cochleae und Apertura Venae canaliculi cochleae bei einem Embryo von 253 mm Sch.-St.-L.

Abb. 2. Apertura externa canaliculi cochleae und die Austrittstelle der Vena canaliculi cochleae bei einem 386 mm langen Fötus.

nude, durch welche die Arterien und Venen zur Labyrinthkapsel hindurch treten, kommt, müssen wir annehmen, dass dadurch auch der Aquaeductus cochleae bzw. der parallel verlaufende Kanal für die V. canaliculi cochleae komprimiert sein wird. Die Kompression der kochlearen Vene, die die Hauptmenge des venösen Blutes aus dem membranösen Labyrinth drainiert, wird zu einer Venostase führen, ebenso wie die Kompression des cochlearen Kanälchens zu einem erschwerten Austausch zwischen der Labyrinthflüssigkeit und dem Liquor führen muss. Die Venostase, die sich durch eine lange Zeitperiode hindurch entwickelt, wird ihrerseits zu einer Störung in der Produktion der Perilymphe, die nach Graf & Poretti (1950) sowie Naftalin & Harrison (1958) durch Ultrafiltration aus dem Blut entsteht, führen. Es wird dadurch notwendig zu einem chronischen Hydrops des Labyrinthes durch eine lange Zeitperiode kommen und dies scheint uns derjenige Faktor zu sein, der für eine Progressivität der Leitungsschwerhörigkeit verantwortlich ist.

Der Aquaeductus cochleae wurde von mehreren Autoren auf seinen Bau und seine Durchgängigkeit beim Kaninchen und Menschen histologisch und experimentell untersucht (Y. Meurman, 1930, Streeter, Karlefors, u. a.).

Winckler (1963) hat den Aquaeductus cochleae bei der Katze, beim Lamm, beim Ochsen und bei menschlichen Föten sowie an erwachsenen Menschen eingehend studiert. Während bei den genannten Säugetieren und beim menschlichen Fötus der Kanal sondierbar ist, kann man ihn beim erwachsenen Menschen schwer sondieren, so dass man ihn mit der Fräse darstellen muss. Er äussert die Meinung, dass der Aquaeductus cochleae beim erwachsenen Menschen so eng ist, um von den Druckschwankungen des Liquors die Perilymphe zu schützen. Delattre hat in der Diskussion richtig bemerkt, dass der abgebogene Verlauf des Canaliculus cochleae beim

Erwachsenen, den Winckler beschreibt, mit der Rotation der Pyramide in Zusammenhang steht. Meurman hat gefunden, dass der Canaliculus cochleae bei Menschen cca 10 mm lang ist und einen Arachnoidealstrang der im engsten Teil des Kanals meist fest ist, enthält Im Anfang und an der Einmündung ist das Bindegewebe locker. Selten kann es durch Endostwucherung zur Obliteration des Kanals in seinem engsten Abschnitt kommen Es besteht nach Meurman die Möglichkeit, dass der Kanal erst nach dem 50 Jahr verengt wird Das Arachnoidealgewebe steht mit der Arachnoidea um den N glossopharyngeus in Zusammenhang

Der Arachnoidealstrang enthält wenige Gefässe Die Vena aquaeductus cochleae geht durch einen eigenen Kanal, der in der Scala tympani breiter und an der Basis der Pyramide enger als die entsprechende Öffnung des Aquaeductus cochleae ist Der engste Abschnitt der beiden ist ungefähr gleich breit Young (1952) hat neulichst an Abgussen vom Schlafenbein feststellen können, dass der Canaliculus cochleae ebenso wie der Canaliculus vestibuli eine sackförmige Erweiterung, die an seinem Ende liegt, bildet

Es muss bei der erwähnten Kompression des Aquaeductus bzw. der Vene nicht zu menièreförmigen Symptomen kommen, da der Hydrops sehr langsam zustande kommt, ähnlich wie sich auch ein chronischer Hydrocephalus langsam ohne alarmante Symptome entwickelt

Einige Tatsachen sprechen fur unsere Ansicht Wenn wir die Öffnung des Aquaeductus cochleae und diejenige fur die Vene an der unteren Seite der Pyramide betrachten, sehen wir, dass die beiden in manchen Fällen sehr verengt sind, ähnlich wie dies Šercer fur den Canaliculus tympanicus feststellen konnte

Einen Beweis, dass es zur Kompression der Kanäle in der Pyramide kommt, haben uns diejenigen Fälle geliefert, wo die Patienten, bei denen die Otosklerose operativ verifiziert war, über einen langdauernden salzigen Geschmack klagten In diesen Fällen handelt es sich sicher um eine Irritation der Chorda tympani wahrscheinlich an der Stelle, wo sie durch den gleichnamigen Kanal zusammen mit der Arteria tympanica posterior hindurchtritt Dass es zu einer Deformation und Dislokation der Kanäle in der Pyramide kommen kann, haben wir mit unseren Beobachtungen bei platybasischen Schädeln bewiesen Wir haben festgestellt, dass es durch Kompression nicht nur zu einer Deformation des Labyrinthes, sondern auch zu einer Dislokation des facialen Kanals gekommen ist.

Noch eine weitere Beobachtung spricht fur unsere Auffassung Man findet manchesmal bei jungen Leuten mit dem klinischen Bild einer Otosklerose bei der Operation weder die Stapesfixation noch die Obturation der Fenestra rotunda und doch fuhrt bei ihnen eine Fenestration zur Besserung des Zustandes

Anderseits fuhrt bei einigen älteren Patienten in Fällen von Otosklerose, wo der Stapes durch Osteophyten fixiert ist, die Fenestration nicht zum gewunschten Erfolg Man muss annehmen, dass in diesen Fällen die Oloskle-



Abb. 3



Abb. 4

Abb. 3. Mit der Fräse auspräparierter Canaliculus cochleae von einem 10jährigen Kind
Abb. 4. Mit der Fräse dargestellter Canaliculus cochleae von einem Erwachsenen

roseherde, die sich in „stillen" Regionen des Labyrinthes oder in der Nähe des Randes des ovalen Fensters (wie dies an einigen Präparaten von Sercer und Krmpotic sichtbar ist) befinden, durch eine lange Zeitperiode das Lumen des Labyrinthes verengen und dieselben Störungen wie die Okklusion der beiden Labyrinthfenster hervorgerufen haben. Wenn die Osteophyten das Lumen vor oder hinter dem ovalen Fenster grösstenteils verlegen, wird das System der Bogengänge von dem übrigen Teil des Labyrinthes praktisch separiert, so dass die Fenestration keinen Effekt auf den akustischen Teil des Labyrinthes haben kann. Ruedi referiert über einige eigene Fälle sowie über einige Literaturangaben (Politzer, Habermann, Nager, Frazer, Mayer), wo man in der Scala tympani in der Basalwindung mit Sicherheit knöcherne Neubildungen im Sinne von osteoidem Saum, Enostosen oder einen knöchernen Block, der die Skala komplett obturierte, feststellen konnte. Die Knochenbildungen können sich auch an der Einmündungsstelle des Aquaeductus cochleae (M. Meyer) bzw. der Vena canaliculi cochleae befinden. Solche Knochenneubildungen müssen einen Hydrops des Labyrinthes zur Folge haben.

Wir müssen daraus schliessen, dass dasjenige operative Verfahren am Labyrinth einen dauernden Effekt haben wird, das neben einer Sicherung der zwei funktionsfähigen Fenster auch eine dauernde Drainage der Labyrinthflüssigkeit garantieren wird. Neben der Tatsache, dass sich die Fenestra novoovalis in einem gesunden Terrain befindet, ist es weiter wichtig, dass das neue Fenster am lateralen Bogengang, nur durch einen zarten tympanomeatalen Lappen gedeckt, eine Fluktuation des labyrinthären Druckes und eine Diffusion der Labyrinthflüssigkeit ermöglichen wird. Bei der Mobilisation besteht selbstverständlich nicht die Möglichkeit einer dauernden Diffusion der Labyrinthflüssigkeit, da die kapilläre Spalte zwischen dem

ovalen Fenster und der Stapesplatte verwachst und das *Durchtreten der* Labyrinthflüssigkeit, unmöglich macht, so dass der Labyrinthdruck immer weiter wegen der erwähnten Kompression vergrössert wird Ob die Fenestration des ovalen Fensters, die Ruedi neulichst mit guten Resultaten verwendet, diesen Bedingungen *entsprechen wird*, *muss noch* an einem grossen Material und durch eine längere Zeitperiode nachgeprüft werden

Wenn wir noch die Beobachtungen von Altmann an Patienten, die kurz nach der Mobilisation verunglückt waren, in Erwägung ziehen, glauben wir, dass auch dies zugunsten einer Fenestration spricht

SUMMARY

The progression of conductive hearing loss in otosclerosis cannot be explained alone by the degree of fixation of the stapes because, when the stapes is fixed *in a greater part* of its circumference, it loses its mobility According to our opinion this progressive loss of hearing is the consequence of a chronical hydrops of the labyrinth which is due to the compression of the aqueductus *cochleae and the corresponding vein in the course of the evolution of the* kyphosis of the base of the skull

RÉSUMÉ

La progression de la surdité de transmission en otosclérose ne peut pas dépendre seulement du grade de la fixation de l'étrier car si celui est fixé dans une partie considérable de sa circonférence il perd déjà sa mobilité Il nous semble que le facteur qui joue le rôle principal est un hydrops chronique du labyrinthe produit par la compression de l'aqueduc du limaçon et de la veine commitante due au développement de la cyphose de la base crânienne

LITERATUR

GRAF K und POKETTL G, 1950 Die Entstehung der Perilymphe *Pract Otorhinolaryng* (Basel) V *12* Fasc 5 6

MEURMAN Y, 1930 Zur Anatomie des Aqueductus cochleae nebst einigen Bemerkungen über dessen Physiologie *Acta societatis medicorum fennicae Duodecim* Toimituksia Ser B *13* Fasc 1

MEYER M, 1939 Eine neue Anschauung über die Schwerhörigkeit bei Otosklerose und vielleicht ein neuer Weg zu ihrer Behandlung *Mschr Ohrenheilk* 2 73

1939 La ponction sous occipitale et son influence sur les hypoacousies dans l'otosclerose et l'atrophie labyrinthique *Ann Otol ryng (Par)* 6

— 1935 Eine neue Anschauung über die Schwerhörigkeit bei Otosklerose und vielleicht ein neuer Weg zu ihrer Behandlung *Acta Otolaryng (Stockh)*, 27 1

NAFTALIN L und HARRISON M S, 1958 Circulation of labyrinthine fluids *J Laryng* 2 118

PORTMANN M und C *Précis d'audiometrie clinique* Masson et Cie Paris 1959

RUEDI L, 1961 Neuentwicklung der Chirurgie der Otosklerose *Deutsch Med Wochenschr* 86 48 S 2305 2309

1961 Histopathologische Veränderungen im Innenohr bei Otosklerose *Fortschr Hals Nas Ohrenheilk* 8 77 112



Abb. 3



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Wenn wir noch die Beobachtungen von *Altmann* an Patienten, die kurz nach der Mobilisation verunglückt waren, in Erwägung ziehen, glauben wir, dass auch dies zugunsten einer Fenestration spricht.

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La progression de la surdité de transmission en otosclérose ne peut pas dépendre seulement du grade de la fixation de l'étrier car si celui est fixe dans une partie considérable de sa circonférence il perd déjà sa mobilité. Il nous semble que le facteur qui joue le rôle principal est un hydrops chronique du labyrinthe produit par la compression de l'aqueduc du limaçon et de la veine commitante, due au développement de la cyphose de la base crânienne.

LITERATUR

Graf, K. und Poretti, G., 1950. Die Entstehung der Perilymphe. *Pract. Otorhinolaryng.* (Basel), V. 12. Fasc. 5–6.

Meurman, Y., 1930. Zur Anatomie des Aqueductus cochleae nebst einigen Bemerkungen über dessen Physiologie. *Acta societatis medicorum fennicae. Duodecim.* Toimituksia Ser. B. 13. Fasc. 1.

Meyer, M., 1939. *Eine neue Anschauung über die Schwerhörigkeit bei Otosklerose und vielleicht ein neuer Weg zu ihrer Behandlung.* Mschr. Ohrenheilk. 2. 73.

1939. La ponction sous occipitale et son influence sur les hypoacousies dans l'otosclérose et l'atrophie labyrinthique. Ann. *Otolaryng.* (*Par.*) 6.

— 1939. Eine neue Anschauung über die Schwerhörigkeit bei Otosklerose und vielleicht ein *neuer Weg zu ihrer Behandlung.* *Acta Otolaryng.* (*Stockh.*) 27. 1.

Naftalin, L. und Harrison, M. S., 1958. Circulation of labyrinthine fluids. *J. Laryng.* 7. 118.

Portmann, M. und C. *Précis d'audiométrie clinique.* Masson et Cie. Paris 1959.

Ruedi, L., 1961. Neuentwicklung der Chirurgie der Otosklerose. *Deutsch. Med. Wochenschr.* 86. 48. S. 2305–2309.

1961. Histopathologische Veränderungen im Innenohr bei Otosklerose. *Fortschr. Hals Nas. Ohrenheilk.* 8. 77. 112.

— 1962 Histopathology of sensorineural degeneration and other inner ear changes in otosclerosis *H Ford Hosp Intern Symposium Otosclerosis 1962*

— 1962 Long term results in the Fenestration operation comparative short term results in stapes mobilisation and interposition operation *H Ford Hosp Intern Symposium Otosclerosis 1962*

Rüedi L und Suter Cs Stapedectomie mit Interposition *Acta Otolaryng* (Stockh) 54

Tonndorf J 1963 Quantitative Analyse der Knochenleitung nach Tierversuchen *Arch Ohr Nas Kehlkopfheilk 182* Bd 2 Heft II Teil Sitzungsbericht 1963

Winckler G 1964 Observations relatives à l'aqueduc du limaçon chez l'homme *Compt rend de l'assoc des Anat XLVIIIe Réunion* (Toulouse 15 19 Avril 1962) Nancy 1964

Young M W 1952 The termination of the perilymphatic duct *Anat Rec 112* 2

Vedarska 97 Zagreb Jugoslavien

EXPERIMENTELLE OTOSKLEROSEFORSCHUNG AM HUND

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Aus dem Anatomischen Institut der Medizinischen Fakultät (Dir. Prof. Dr. I. Krmpotić) und dem Institut für die Erforschung und den Schutz des Ohres und der oberen Luftwege (Dir. Prof. Dr. A. Šercer) Zagreb

Dem Verfasser ist es gelungen, bei sieben Hunden biologisch eine Knickung der Schädelbasis um 3–5 Grad zu erreichen. Der durch Angulation der Schädelbasis hervorgerufene Druck des umgebenden Knochens auf den Labyrinthkern rief in der *enchondralen Schicht der Kapsel* einen Umbau des Knochens hervor. In einem Falle resultierte daraus eine fibröse und in einem anderen sogar eine osteofibröse Fixation des Stapes. — Demonstration von Diapositiven.

Da alle Bemühungen der besten Kenner der Knochenpathologie, wie Nager, O. Mayer, Wittmaack, M. Meyer, Weber, Fowler, Altmann und anderer, nicht zur endgültigen Klärung der Frage der Ätiologie der Otosklerose führen konnten, haben sich neuere Forscher (Arslan und Mitarbeiter, Arduoin, Chevance, 1962) dem Studium der Biochemie und der Histochemie *des otosklerotischen Herdes zugewandt.*

Obwohl diese Untersuchungen zu wertvollen Resultaten führten, dürfen *wir doch nicht voraussetzen und auch nicht erwarten, dass bisherige* Erkenntnisse durch erwähnte neue Untersuchungen als gegenstandslos gewertet oder als wertlos gestrichen werden müssen. Weit davon! Die nur ein Jahr nach dem Kongresse in Paris publizierten biochemischen Untersuchungen von Altmann, Holdsworth und Bloch von der Columbia Universität (New York) *berichten über vollkommen negative* diesbezügliche Resultate und lassen uns leider ziemlich skeptisch auf dieses Arbeitsgebiet blicken.

Chevance, sicher einer der besten Kenner der Biochemie des Otosklerosehеrdes, sucht in der chemischen Analyse der Otosklerose nicht eine grundlegend neue Erkenntnis, sondern eine Vertiefung und Zergliederung unserer bisherigen Erkenntnisse, um das Wesen der Krankheit besser erblicken *zu können.* Chevance sagt ja ausdrücklich: „Der Aufbau des Knochens, welcher zur histologischen Heilung des Herdes und gleichzeitig zur Ankylose des Stapes führt, erscheint biochemisch, histochemisch, sogar morphologisch viel näher der Physiologie als der Pathologie zu sein; diese Erkenntnis führt uns natürlich zum Ausgangspunkt unserer Ausführungen, d. h. zur destruktiven Periode oder wenigstens zur initialen Phase der Otosklerose. Schon Siebenmann und viele andere Autoren haben vor Jahren darauf aufmerksam gemacht, dass die Anfangserscheinungen der Otosklerose in den Knorpelzellen zu suchen sind. Ihre Häufigkeit in der Labyrinthkapsel ist uns gut bekannt." Soweit Chevance.



Abb 1 Querschnitt durch den vertikalen halbzirkelformigen Kanal (Lupenvergrosserung 20 ×) Der Kanal ist innen mit einer schmalen Zone kompakten Knochens umgeben Nach aussen folgt eine breite Zone des Knochens im Umbau, wo man unregelmassige Gruppen verknochernder Knorpelzellen sicht An gewissen Punkten sieht man Stellen die leer erscheinen und der ungefarbten Grundsubstanz entsprechen Rings um diesen Knochen befindet sich normaler kompakter Knochen

Ist es notwendig, an dieser Stelle noch andere in dieselbe Richtung zielende Ansichten, wie z B die von Cawthorne zu zitieren? Wir glauben nicht, weil uns die schon bisher zitierten Ansichten an den Rand der Erkenntnis gefuhrt haben

Wir konnen aber auf Grund unserer anthropologischen Studien zu den oben erwähnten Untersuchungsresultaten noch folgende Gedanken hinzufugen

Der fruhe Stillstand des Verknocherungsprozesses der Labyrinthkapsel im zweiten Lebensjahre ist durch funktionelle Grunde des inneren Ohres bedingt Die Labyrinthkapsel erreicht namlich ihre definitive Form und Grosse bereits am Ende des zweiten Lebensjahres, gerade zur Zeit als die Myelinisation der zentralen Nervenbahnen beendet ist, welche die Funktion des Gehors und der Sprache, des Gleichgewichtes und des aufrechten Ganges koordinieren Nach dieser Periode darf die Labyrinthkapsel weder wachsen noch ihre Form ändern, weil dadurch ihre Funktion geschadigt wurde Zu dieser Zeit ist aber der Labyrinthknochen noch unreif und enthalt in 60% der Falle embryonales Knorpelgewebe an uns gut bekannten Stellen Der normale Knochen wächst aber bis zum 18 oder 20 Lebensjahre Nach Beendigung der Entwicklungsperiode wird der Knochen bis zum Ende



Abb. 2. Ein Flachschnitt durch denselben Kanal. Stärkere Vergrösserung (ungefähr 60×). Rings um den Bogengang ist der Knochen im Umbau. Der umgebende Knochen ist dagegen kompakt.

des Lebens ständig umgebaut und er akkommodiert sich fortwährend allen mechanischen Beanspruchungen.

Der Labyrinthkern erstarrt dagegen zeitlebens in seiner embryonalen Form. Nach dem jähen Stillstand des Wachstums der Labyrinthkapsel, welcher am Ende des zweiten Lebensjahres eintritt, treibt ein neuer Reiz die in Entwicklung zurückgebliebenen Partien des Labyrinthknochens zur Beendigung des im embryonalen Leben begonnenen Verknöcherungsprozesses. Dieser neue Reiz ist die durch aufrechten Gang hervorgerufene starke Knickung der Schädelbasis und der dadurch ausgeübte Druck auf die Labyrinthkapsel. Der Einfluss von Druck und Dehnung auf die Struktur des Knochens ist nach langen Diskussionen (Triepel, Wolff, Weidenreich usw.) von Murray (1936) folgendermassen formuliert worden:

Unter normalen Verhältnissen sind innere Kräfte von entscheidender *Bedeutung für das Wachstum und für die Form des Knochens. Unter ab*normen Zuständen, z. B. beim Nichtgebrauch oder bei Überlastung des Knochens, haben dagegen die äusseren Kräfte einen überwältigenden Einfluss auf die Umformung der Knochensubstanz (Sissons).

Das Resultat der mechanischen Kräfte ist von verschiedenen Faktoren abhängig: von der Intensität des Druckes, von der Qualität des Knochens und von der Lage des Labyrinthkernes in der Schädelbasis.

In Anbetracht der Überlegungen, welche Ruedi in seinem Vortrage über die Pathogenese der Otosklerose (in Chicago 1961) auseinandergelegt hatte und welche wir vollauf anerkennen, müssen wir unsere bisher starr vertre-



Abb. 3. Vergleich eines quer durchschnittenen Bogenganges mit einem Nest Zellgewebe, welches vom kompakten Knochen umgeben ist.

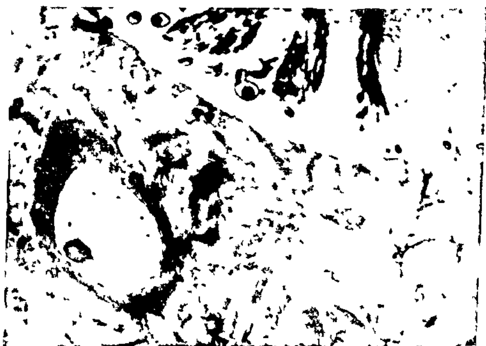


Abb. 4. Silberimprägnation desselben Präparates (nach Gomori). Man vergleiche den kompakten Knochen der Umgebung mit der an Fibrillen sehr reichen inneren Schichte des quer durchschnittenen Bogenganges. Ausserhalb dieser Zone befindet sich der Knochen im Umbau. Diese Gegend ist stellenweise, je nach dem Alter des Knochens, verschieden stark mit Silber imprägniert.



Abb 5 Man sieht das Ringband mit welchem der Stapes am Rand der Fenestra ovalis verbunden ist Die eine Seite des Ligaments ist normal wogegen auf der anderen Seite arthrotische Veränderungen zu sehen sind welche sich in Unregelmässigkeiten und in Wucherung des fasrigen Gewebes zeigen Das Bild entspricht einer bindegewebigen Ankylose Auffallend ist eine Verdickung des Promonturiums und Vertiefung der Stapesplatte

Eine Meinung über den Einfluss der Venostase insofern andern, als wir zugeben müssen dass eine erhöhte Sättigung des durch die Labyrinthkapsel fliessenden Blutes mit osteophylen Hormonen nicht immer unbedingt notwendig ist um eine Reaktion im Knochen hervorzurufen Der *durch Druck Zug oder Torsion umgestimmte Knochen reagiert biologisch* anders auch auf normale Quantitäten von cirkulierenden Hormonen *im Blute* Es ist ein physiologisches Gesetz, dass ein durch äussere *Einflüsse biologisch* modifiziertes Gewebe auf normalen Hormongehalt im Sinne einer Hyperästhesie reagiert

Theoretisch ist unsere anthropologische Hypothese durch folgende Erkenntnisse *unterstützt*

1 *Die Otosklerose* ist eine spezifische Erkrankung des Menschen Bei Tieren existiert sie nicht



Abb 6 Dasselbe Präparat bei stärkerer Vergrösserung (ungefähr 70×) Der Unterschied zwischen rechts und links ist deutlich zu sehen

2 Nur beim Menschen ist infolge des aufrechten Ganges die Schädelbasis geknickt

3 Der otosklerotische Prozess erscheint nur an der Labyrinthkapsel, in anderen Korperknochen aber nicht

4 Dieser Prozess entwickelt sich vorwiegend gleichzeitig an beiden Seiten und an symmetrischen Stellen der Labyrinthkapsel

Diese grundlegenden Indizien der anthropologischen Theorie, von uns jahrelang studiert und durchdacht, erforderten doch eine experimentelle Begrundung

Fur unsere Versuche wählten wir Hunde, und zwar aus zwei Grunden Bei Hunden enthalt die Labyrinthkapsel, ebenso wie beim Menschen, beträchtliche Knorpelreste, was bei der Entstehung der Otosklerose von grundlegender Bedeutung ist M Weber sagt doch in seiner letzten Arbeit uber Otosklerose und Knorpel der Labyrinthkapsel (1961) „Die späte und verzogerte Ossifikation liegengebliebener Knorpelreste erklärt die Entstehung der Otosklerose an ganz bestimmten Punkten der Labyrinthkapsel im postfötalen Alter" Und nach weiteren Überlegungen sagt er „Die letzte Frage ist jetzt was verursacht denn die spate Ossifikation der Knorpelreste aus der Embryonalzeit oder des neugebildeten neoplastischen Knorpels ?"

Ausserdem ist bei Hunden der Labyrinthkern fest in der Pyramide und in der Schadelbasis verankert, womit das Hundelabyrinth dem menschlichen Labyrinth seinem Bau und seiner Lage nach sehr nahe kommt

Es galt nun bei jungen Hunden eine Knickung der Schädelbasis hervor-



Abb. 7. Die kranke Seite des Ringbandes bei stärkerer Vergrösserung (ungefähr 300 ×). Das Ligament ist nicht nur fibrös durchwuchert, sondern auf der Aussenseite sowie auf der Innenseite ist ein Plättchen frischen Knochens zu sehen.



Abb. 8. Der zweite Fall. Eine Seite des stapedovestibulären Gelenkes zeigt ausgesprochene Veränderungen im Sinne einer osteofibrösen Ankylose. Eine buckelförmige Verdickung (Exostose ?) des Promunturiums hat zur Deformierung eines Schenkels des Steigbügels geführt. Auffallend ist die Verdickung eines Schenkels und der Stapesplatte.



Abb 9 Derselbe Fall bei stärkerer Vergrösserung Die Ankylose ist deutlich zu sehen

zurufen Unsere Experimente begannen wir im Frühjahr 1961 Nach langen Überlegungen und Versuchen gelang es uns, bei sieben Hunden (im Alter von 6 Wochen, immer aus demselben Wurf) durch Kauterisierung der oberen Hälfte der Kornea signifikante Änderungen der Schädelbasis hervorzurufen Die operierten Hunde wurden dadurch gezwungen, den Kopf ständig hoch zu halten, um sich in der Umgebung orientieren zu können Infolge von Änderung der Lage des Kopfes im Raume rief die Gravitation einen stärkeren Zug auf die vordere Partie des Kopfes, als es unter normalen Umständen der Fall ist, wenn der Kopf von der Wirbelsäule nach unten hängt Bereits 9 bis 12 Monate nach dem Versuchsbeginn stellten wir eine Biegung der Schädelbasis um 3–5 Grad fest, was vom anthropologischen Standpunkt betrachtet sehr signifikant ist

An dieser Stelle wollen wir bemerken, dass sich der amerikanische Anatom Moss ebenfalls seit 1961 mit dem Gedanken beschäftigte, ob es möglich wäre, experimentell die Form der Schädelbasis bei Tieren zu ändern Der Autor beobachtete eine deutliche Knickung der Schädelbasis bereits 90 Tage nachdem er den weissen Ratten die vorderen Extremitäten nach der Geburt abschnitt und so die Tiere zwang, sich auf den Hinterbeinen aufrecht zu bewegen Moss studierte dabei die Funktion des Labyrinthes, welches in der Schädelbasis der Ratte elastisch eingebettet ist Er konnte die Behauptung von Delattre und Fenart bestätigen, dass das Labyrinth ein Stabilisator des Kopfes im Raume ist Ratten waren für unsere Experimente nicht geeignet Wir brauchten Tiere, bei welchen das Labyrinth in die Schädelbasis fest eingeschlossen ist und bei welchen sich die auf die Schä-



Abb. 10. Querschnitt durch die Pyramis des Vestibulums. Der Knochen ist aus Herden verknöchernder Knorpelzellen zusammengesetzt. Man sieht viele optisch leere Räume. Es handelt sich um die Auflösung oder um die Nichtfärbung der organischen Knochengrundsubstanz.

delbasis einwirkenden Kräfte folglich auf den Knochen des Labyrinthes übertragen müssen.

Aus früheren Studien wussten wir, dass Verbiegungen der Schädelbasis bloss um einen Grad bereits deutliche Änderungen des Nasenseptums hervorrufen können. Da sich das Labyrinth an der empfindlichsten Stelle der Schädelbasis (Delattre und Fenart) befindet, waren auch am Labyrinthe Strukturveränderungen zu erwarten.

e histologische Bilder aus unserer dies
chreiben und zu demonstrieren. Aus
wir aber nur einige Bilder.

Am Ende dieser Beobachtungen stellt sich die Frage: Wie soll man die beobachteten Veränderungen auswerten? Wir möchten uns dabei nicht übereilen. Vor einer endgültigen Schlussfolgerung wollen wir auf entsprechende Gedanken von Leriche und Chevance aufmerksam machen. In seiner Philosophie der Chirurgie sagt Leriche, dass es mehrere Krankheiten gibt, welche man nur am Menschen studieren kann, weil keine Möglichkeit besteht, dieselben am Tiere zu provozieren. Chevance (in seiner Histochemie der otosklerotischen Herde) hat andererseits auf die grossen Unterschiede in der Struktur der menschlichen und der tierischen Labyrinthkapsel aufmerksam gemacht.

Im Jahre 1959, in einer Arbeit über die Otosklerose im Tierreich haben



Abb. 11. Querschnitt durch die Wand der Schnecke. Die Schnecke ist mit einer dünnen Schicht des endostalen kompakten normalen Knochens umgeben. Nach aussen folgt eine breite Zone des Knochens im Umbau. Da sieht man einige unregelmässige Gruppen verknöchernden Knorpels.

wir schon behauptet, dass die Labyrinthkapsel des Hundes ihrer Struktur nach derjenigen des Menschen am nahesten steht. Die erzielten Resultate der experimentellen Forschung muss man also auch von diesem Standpunkte aus beurteilen.

Deswegen erlauben wir uns, aus unseren bisherigen Studien sowie aus beschriebenen Versuchen, folgende Schlussfolgerungen zu ziehen.

1. Wir glauben behaupten zu dürfen, dass die Otosklerose beim Menschen als Resultat einer verspäteten, nachträglichen, mechanisch bedingten und einer nicht mehr biologisch dirigierten aber hormonal beeinflussten Ossifikation der Labyrinthkapsel zu betrachten ist. Dieser Prozess gehört also in das Gebiet der Entwicklungsstörungen.

Die primären Erscheinungen bei der Entstehung der Otosklerose sind die im postembryonalen Leben einsetzende Verknöcherung der in der Labyrinthkapsel zurückgebliebenen embryonalen Knorpelreste und der durch dieselben Kräfte bedingte Umbau des bereits gebildeten Labyrinthknochens.



Abb 12 Ein Detail des Knochenumbaus aus demselben Präparat Man sieht eine Gruppe von Knorpelzellen von einer Zone Osteoids umgeben an welches sich neugebildeter kompakter Knochen anschliesst (Vergrösserung ungefähr 600 ×)

Die otosklerotischen Erscheinungen in der Labyrinthkapsel des Menschen sind also Folgen der mechanischen Kräfte und der damit verbundenen hormonalen Einwirkung auf den Labyrinthknochen

2 Im Laufe von 9 bis 12 Monaten ist es uns gelungen, bei jungen Hunden eine Knickung der Schädelbasis (Angulation) von 3–5 Grad zu provozieren was zu signifikanten Änderungen an der Labyrinthkapsel der Tiere führte Eine Hyperämie im Labyrinthknochen wurde oft, aber nicht immer, beobachtet

3 *Es ist zwar eine biologische Erfahrung, dass die Gleichförmigkeit der* Gewebestruktur nicht immer die gleiche Ursache haben muss (Isomorphie bedeutet nämlich nicht immer Homogenie) Im konkreten Falle können wir aber die Veränderungen in der Labyrinthkapsel der Hunde nur mit Veränderungen, die an ihrer Schädelbasis entstanden sind, in Zusammenhang bringen

4 Histologische Veränderungen bei unseren Versuchstieren haben wir nur in der enchondralen Schicht beobachtet, während die endostale Schicht sowie die periostale normal blieben

a In der mittleren Schicht der Labyrinthkapsel findet man eine unregelmässige Ossifikation auf Grund von Nekrose der Grundsubstanz (wie im Anfangsstadium der Otosklerose?), weiterhin eine Vermehrung und eine Verdickung der Balken des spongiösen Knochens (wie im Blütestadium

der Otosklerose?), und schliesslich eine Verdichtung der Knochenbalken (wie im Endstadium der Otosklerose?).

6. In zwei Fällen fand man eine fibröse, ja sogar eine osteofibröse einseitige Fixation des Stapes.

7. Wir stellen fest, dass beim Hunde bereits am Ende des ersten Jahres die Verknocherung der Labyrinthkapsel beendet ist, dass aber noch beim 7jährigen Hunde Knorpelreste am Rande des ovalen Fensters festzustellen sind, was die Meinung bestätigt, dass gerade der Hund für die experimentelle Otoskleroseforschung am besten geeignet ist.

8. Wir glauben feststellen zu dürfen, dass die histologischen Veränderungen den Beobachtungen bei der menschlichen Otosklerose sehr ähnlich, obwohl nicht vollkommen identisch, sind.

Es scheint uns aber, dass schon diese Feststellung genugt und unsere Schlussfolgerung berechtigt, dass die bisherigen Resultate unserer experimentellen Untersuchungen zugunsten der anthropologischen Theorie über die Entstehung der Otosklerose sprechen.

SUMMARY

The author succeeded to produce in 7 dogs a biological kyphosis of the base of the skull for 3–5 degrees. The pressure of the surrounding bone caused by the angulation of the base of the skull produced in the enchondral layer of the labyrinthine capsule a reconstruction of the bone resulting in one case in a fibrous and in the other case in an osteofibrous fixation of the stapes — Demonstration of slides.

RÉSUMÉ

L'auteur est parvenu, dans des délais de 7 à 12 mois, à provoquer par voie biologique, sur sept jeunes chiens, une angulation de la base de leur crânes variant de 3 à 5 degrés La pression exercée sur le noyau labyrinthique par suite du pliage de la base crânienne, a provoqué dans tous le cas un remaniement de l'os dans la couche enchondrale de la capsule Dans un cas il en est arrivé à la fixation fibreuse de l'étrier, dans un autre, cette fixation était même osteofibreuse. — Démonstration des diapositives

Novakova 17 Zagreb, Jugoslawien

DIE EIGENFREQUENZEN DES SCHADELS UND IHRE AUDIOMETRISCHEN AUSWIRKUNGEN

H J Borecki
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Die Eigenfrequenz des menschlichen Schadels wurde erstmalig von v Bekesy bestimmt Er fand einen Wert von etwa 1800 Hz In neuester Zeit hat Kirikae das *Problem der Eigenfrequenz* des Schadels außerordentlich exakt untersucht Er fand — wie das bei einem so kompliziert zusammengesetzten Gebilde wie es der Schadel ist der ja physikalisch ein System miteinander gekoppelter schwingungsfahiger Korper darstellt — zahlreiche Eigenfrequenzen Die erste bestimmte er in Uber *einstimmung mit v Bekesy zu 1800 Hz* Des weiteren fand er Eigenfrequenzen bei 2000 Hz 2400 Hz 2700 Hz 3000 Hz 3200 Hz 3500 Hz 3600 Hz 4000 Hz und daruber Diese Untersuchungen veranlaßten uns einmal die selektierende Wirkung des menschlichen Schadels in bezug auf Tone bzw Rauschen zu untersuchen

METHODIK

Am rechten Felsenbein eines Knochenschadelpraparates wurde mit Uhuhart ein Beschleunigungsempfanger (Rohde & Schwarz Type EBM B BN 432111) dessen Eigenfrequenz oberhalb von 20 kHz lag befestigt Dieser war uber einen Mikrophonverstarker (Rohde & Schwarz BN 483023) mit einem Tonfrequenzanalysator (Rohde & Schwarz Type FTA BN 48302) verbunden dessen Bandbreite + 6 Hz bei 3 dB Abfall bzw ± 40 Hz bei 60 dB Abfall betrug Am Ausgang des Tonfrequenzanalysators wurde ein Gleichspannungsschreiber (Rohde & Schwarz Type ZSG BN 18531) angeschlossen *dessen Papiervorschub synchron mit der Frequenzeinstellung* des Analysators lief Uber einen nacheinander an verschiedenen Stellen des Schadels durch Klemmbugel angekoppelten Knochenschallgeber (Jaquet Basel) wurden zunachst aus einem mit dem Tonfrequenzanalysator gekoppelten Mitlaufgenerator (Rohde & Schwarz BN 483011) Sinustone gegeben, deren Frequenzen mit der jeweiligen Durchlaßfrequenz des Analysators uber einstimmten und danach uber einen Rauschgenerator (Atlas LA 47) ein weißes Gerausch Die dadurch verursachten *erzwungenen Schwingungen* des Schadels wurden am Felsenbein abgeleitet und frequenzanalysiert dem Gleichspannungsschreiber zugefuhrt, der sie in einem Frequenz Amplituden

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Novakova 17, Zagreb, Jugoslavien

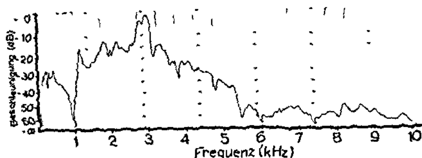


Abb. 2 Beschleunigungs-Frequenz-Diagramm der durch reine Töne konstanten Schalldrucks erzwungenen Schädelschwingungen

sungen bei 1200 Hz. Der Schädel besitzt eine große Anzahl von Eigenfrequenzen, von denen die zwischen 1200 Hz und etwa 4000 Hz liegenden die größte Amplitudenerhöhung bewirken. Das absolute Amplitudenmaximum wird bei ungefähr 3000 Hz erreicht. Die Lage dieses absoluten Maximums ist ebenso wie die Lage der Eigenfrequenzen überhaupt nur unwesentlich von dem Ort der Ankopplung des Knochenschallgebers abhängig. Die eben geschilderten Erscheinungen treten auch auf, wenn der Schädel durch starken Luftschall zu erzwungenen Schwingungen erregt wird (Abb. 2).

2. Erregt man den Schädel durch ein über Knochenleitung zugeführtes weißes Rauschen zum Schwingen, also durch einen Schall, der sich aus Sinusschwingungen aller Frequenzen zwischen 20 Hz und 20 000 Hz mit untereinander gleichen Amplituden und statistisch verteilten Phasenwinkeln zusammensetzt, so sind die dadurch erzwungenen Schädelschwingungen nicht mehr adäquat diesem weißen Geräusch. Die resultierende Schädelschwingung enthält zwar auch Sinusschwingungen aller Frequenzen zwischen 20 Hz und 20 000 Hz, jedoch nicht mehr mit untereinander gleichen Amplituden. Vielmehr sind die Amplituden derjenigen Teilschwingungen, deren Frequenzen mit den Eigenfrequenzen des Schädels übereinstimmen, wesentlich größer als die der übrigen Teilschwingungen. Die einzelnen Frequenzen des weißen Geräusches werden also vom Schädel unterschiedlich

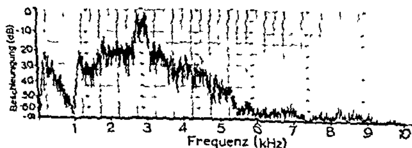


Abb. 3 Beschleunigungs-Frequenz-Diagramm der durch ein weißes Rauschen erzwungenen Schädelschwingungen

Diagramm aufzeichnete. In diesem Diagramm wurden die Eigenfrequenzen des Schädels als Amplitudenmaxima (bzw. -minima) sichtbar.

Danach wurde der Schädel in einer camera silenta starken, über Luftschall zugeführten Tönen, deren Frequenzen mit der jeweiligen Durchlaßfrequenz des Analysators übereinstimmten, und danach einem starken weißen Rauschen (110 dB) ausgesetzt und auf diese Art ohne direkte Ankopplung eines Schallgebers zu Schwingungen erregt. Die Schädelschwingungen wurden wie oben beschrieben registriert.

Bei jeder der beschriebenen Versuchsanordnungen wurden zunächst Eichkurven aufgenommen, um evt. vorhandene Eigenfrequenzen der Übertragungssysteme aus dem endgültigen Ergebnis auszuklammern.

Um die auf diesem Wege objektiv gefundenen Eigenfrequenzen des menschlichen Schädels auch in ihren subjektiven Auswirkungen zu untersuchen, wurden 10 jüngere, audiometrisch geübte Versuchspersonen nach folgenden Schema audiometriert:

1. Aufnahme der normalen Luftleitungshörschwelle des rechten Ohres zur Feststellung der Normalhörigkeit.

2. Aufnahme der Mithörschwelle des rechten Ohres, wenn gleichzeitig auf dasselbe Ohr ein gleichmäßig verdeckendes Rauschen von 50 dB über Luftleitung zugeführt wird.

3. Aufnahme der Mithörschwelle des rechten Ohres, wenn gleichzeitig über Knochenleitung ein gleichmäßig verdeckendes Rauschen zugeführt wird. Dieses Knochenleitungsrauschen wurde dabei zuvor von der jeweiligen Versuchsperson subjektiv auf gleiche Lautstärke wie das 50 dB-Luftleitungsrauschen aus Versuchsanordnung 2 eingestellt.

ERGEBNISSE

1. Erregt man den Schädel über einen Knochenschallgeber mit Tönen verschiedener Frequenzen zu erzwungenen Schwingungen, so tritt bei bestimmten Frequenzen eine deutliche Vergrößerung der Amplitude der Schädelschwingungen (in unserem Fall am rechten Felsenbein gemessen) auf. Die Lage dieser Amplitudenmaxima gibt die verschiedenen Eigenfrequenzen des Schädels an. Die tiefste Eigenfrequenz lag bei unseren Mes-

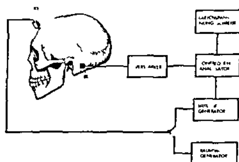


Abb. 1. Schematische Darstellung des Versuchsaufbaus

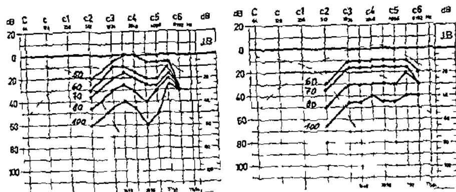


Abb 6 Mithörschwelle für ein über Luftleitung zugeführtes gleichmäßig verdeckendes Rauschen *Links* Die Versuchsperson trägt einen Gehörschutz, der nur die Ohren bedeckt *Rechts* Der Schädel der Versuchsperson ist zusätzlich mit schallabsorbierendem Material umkleidet (Parameter Geräuschintensität in dB)

dort ansteigen, was sich in der allgemein üblichen Hörverlustdarstellung als Senke zeigt (Abb 4) Dieses Ergebnis mahnt zur Vorsicht bei der Anwendung von Knochenschall in der Audiometrie Bei der Tonaudiometrie sind diese auf den Eigenfrequenzen des Schädels beruhenden Amplitudenüberhöhungen durch die Eichung des Tonaudiometers ausgeglichen Dagegen tritt aber eine unkontrollierbare Verzerrung auf, wenn man ohne weitere Vorkehrungen Rauschen oder Sprache über Knochenleitung gibt

Auch ein lauter Luftleitungsschall vermag wie schon erwähnt, den Schädel in Schwingungen zu versetzen, sich also in Knochenschall umzuwandeln Man schützt sich gegen zu lauten, also schädlichen Luftschall z a durch Gehörschützer Die durch sie bewirkte Schalldämmung ist meist frequenzabhängig in der Form, daß tieffrequente Töne weniger stark, Töne mittlerer und höherer Frequenzen aber besonders stark abgeschirmt werden Tamura und Kushida fanden nun kürzlich bei Untersuchungen über Lärmschäden bei Werftarbeitern die mit Gehörschützern arbeiten wider Erwarten Lärmschäden in Form von Senken oberhalb c und schlossen daraus daß die schädigende Schallenergie vorwiegend über Knochenleitung dem Ohr zugeführt wurde Wir sind der Ursache dieser Lärmschäden nachgegangen und haben folgendes Experiment durchgeführt

Zehn normalhörende audiometrisch geübte, jüngere Versuchspersonen wurden nacheinander mit einem Gehörschützer, in dessen einer Muschel ein normaler Audiometerkopfhörer eingebaut war, versehen und einem aus einem Lautsprecher kommenden gleichmäßig verdeckenden Rauschen verschiedener Intensitäten ausgesetzt Nun wurden über den eingebauten Kopfhörer die Mithörschwellen für dieses Rauschen gemessen Es ergaben sich als Durchschnittswerte die in Abb 3 dargestellten Kurven In dieser Absolutdarstellung ergaben sich also nicht, wie zunächst erwartet gerade Mithörschwellen Vielmehr wurden von einer Geräuschlautstärke von etwa 60 dB an Senken im Bereich von 3000 Hz festgestellt deren Tiefe mit der Ge

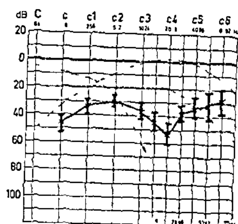


Abb 4

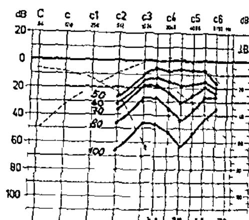


Abb 5

Abb. 4 Mittelwert der Mithörschwellen von 10 Versuchspersonen für ein über Knochenleitung zugeführtes gleichmäßig verdeckendes Rauschen

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bewertet Der Schädel verzerrt das weiße Geräusch gemäß seinen Eigenfrequenzen (Abb 3) Unabhängig von der Ankopplungsstelle des Knochenschallgebers und auch dann, wenn der Schädel in das freie Schallfeld eines starken weißen Rauschens gebracht, also durch Luftschall zum Schwingen erregt wird, werden besonders die Frequenzen zwischen 1200 Hz und 4000 Hz bevorzugt Die Teilschwingungen, deren Frequenzen in diesem Bereich liegen, besitzen also die größten Amplituden Das absolute Maximum liegt bei 3000 Hz

3 Die Bevorzugung der mit den Eigenfrequenzen des Schädels übereinstimmenden Teilschwingungen eines weißen Geräusches durch den menschlichen Schädel läßt sich audiometrisch nachweisen Zehn normalhörende, audiometrisch geübte, jüngere Versuchspersonen wurden nach dem oben erwähnten Schema audiometriert Ihre Luftleitungsmithörschwellen für ein über Luftleitung zugeführtes gleichmäßig verdeckendes weißes Rauschen von 50 dB waren wie zu erwarten Gerade, die im Audiogramm bei Absolutdarstellung auf der 50 dB-Ordinate verliefen Bot man dagegen den Versuchspersonen ein gleichmäßig verdeckendes Rauschen, das vorher von ihnen mit einem 50 dB-Luftleitungsrauschen verglichen und auf gleiche subjektive Lautstärke eingestellt wurde, über Knochenleitung und gab den Prüfton über Luftleitung, so ergaben sich Mithörschwellen, die im Bereich von c^4 (~2000 Hz) deutliche Senken von 10–30 dB aufwiesen Nur diese Senken lagen im Bereich der 50 dB-Ordinate, während der übrige Teil der Mithörschwelle oberhalb 50 dB verlief Diese Senke liegt nun gerade in dem Frequenzbereich, in dem, wie oben ausgeführt, bei erzwungenen Schädelschwingungen die größten Amplituden auftreten Ein über Knochenleitung zugeführtes Rauschen vertäubt also in diesem Gebiet stärker als in anderen Frequenzbereichen Dadurch muß aber notwendigerweise die Mithörschwelle

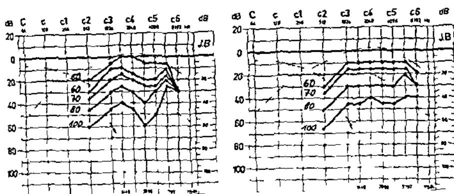


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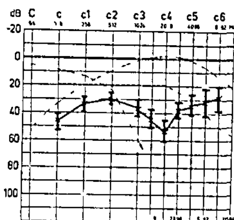


Abb. 4

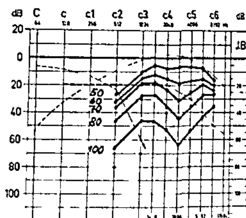


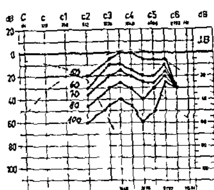
Abb. 5

Abb. 4. Mittelwert der Mithörschwellen von 10 Versuchspersonen für ein über Knochenleitung zugeführtes gleichmäßig verdeckendes Rauschen.

Abb. 5. Mithörschwellen für ein über Luftleitung zugeführtes gleichmäßig verdeckendes Rauschen verschiedener Intensitäten. Die Versuchsperson trägt einen handelsüblichen nur die Ohren bedeckenden Gehörschutz. (Parameter: Geräuschintensität in dB.)

bewertet. Der Schädel verzerrt das weiße Geräusch gemäß seinen Eigenfrequenzen (Abb. 3). Unabhängig von der Ankopplungsstelle des Knochenschallgebers und auch dann, wenn der Schädel in das freie Schallfeld eines starken weißen Rauschens gebracht, also durch Luftschall zum Schwingen erregt wird, werden besonders die Frequenzen zwischen 1200 Hz und 4000 Hz bevorzugt. Die Teilschwingungen, deren Frequenzen in diesem Bereich liegen, besitzen also die größten Amplituden. Das absolute Maximum liegt bei 3000 Hz.

3. Die Bevorzugung der mit den Eigenfrequenzen des Schädels übereinstimmenden Teilschwingungen eines weißen Geräusches durch den menschlichen Schädel läßt sich audiometrisch nachweisen. Zehn normalhörende, audiometrisch geübte, jüngere Versuchspersonen wurden nach dem oben erwähnten Schema audiometriert. Ihre Luftleitungsmithörschwellen für ein über Luftleitung zugeführtes gleichmäßig verdeckendes weißes Rauschen von 50 dB waren wie zu erwarten Gerade, die im Audiogramm bei Absolutdarstellung auf der 50 dB-Ordinate verliefen. Bot man dagegen den Versuchspersonen ein gleichmäßig verdeckendes Rauschen, das vorher von ihnen mit einem 50 dB-Luftleitungsrauschen verglichen und auf gleiche subjektive Lautstärke eingestellt wurde, über Knochenleitung und gab den Prüfton über Luftleitung, so ergaben sich Mithörschwellen, die im Bereich von c⁴ (~2000 Hz) deutliche Senken von 10–30 dB aufwiesen. Nur diese Senken lagen im Bereich der 50 dB-Ordinate, während der übrige Teil der Mithörschwelle oberhalb 50 dB verlief. Diese Senke liegt nun gerade in dem Frequenzbereich, in dem, wie oben ausgeführt, bei erzwungenen Schädelschwingungen die größten Amplituden auftreten. Ein über Knochenleitung zugeführtes Rauschen vertaubt also in diesem Gebiet stärker als in anderen Frequenzbereichen. Dadurch muß aber notwendigerweise die Mithörschwelle



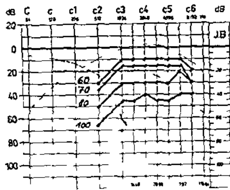


Abb 6 Mithörschwelle für ein über Luftleitung zugeführtes gleichmäßig verdeckendes Rauschen *Links* Die Versuchsperson trägt einen Gehörschutz, der nur die Ohren bedeckt *Rechts* Der Schädel der Versuchsperson ist zusätzlich mit schallabsorbierendem Material umkleidet (Parameter Geräuschintensität in dB)

dort ansteigen was sich in der allgemein üblichen Hörverlustdarstellung als Senke zeigt (Abb 4) Dieses Ergebnis mahnt zur Vorsicht bei der Anwendung von Knochenschall in der Audiometrie Bei der Tonaudiometrie sind diese auf den Eigenfrequenzen des Schädels beruhenden Amplitudenüberhöhungen durch die Eichung des Tonaudiometers ausgeglichen Dagegen *tritt aber eine unkontrollierbare Verzerrung auf* wenn man ohne weitere Vorkehrungen Rauschen oder Sprache über Knochenleitung gibt

Auch ein lauter Luftleitungsschall vermag, wie schon erwähnt den Schädel in Schwingungen zu versetzen, sich also in Knochenschall umzuwandeln Man schützt sich gegen zu lauten, also schädlichen Luftschall u a durch Gehörschützer Die durch sie bewirkte Schalldämmung ist meist frequenzabhängig in der Form daß tieffrequente Töne weniger stark, Töne mittlerer und höherer Frequenzen aber besonders stark abgeschirmt werden Tamura und Kushida fanden nun kürzlich bei Untersuchungen über Lärmschäden bei Werftarbeitern die mit Gehörschützern arbeiten wider Erwarten Lärmschäden in Form von Senken oberhalb c und schlossen daraus daß die schädigende Schallenergie vorwiegend über Knochenleitung dem Ohr zugeführt wurde Wir sind der Ursache dieser Lärmschäden nachgegangen *und haben folgendes Experiment durchgeführt*

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rauschlautstärke zunahm. Es sei ausdrücklich bemerkt, daß sich diese Senken nicht etwa durch den Frequenzgang des Lautsprechers oder des Gehörschützers ergeben haben! Aus diesem Versuchsergebnis kann geschlossen werden, daß *erstens* der Luftschall bei genügender Stärke den Schädel zum Schwingen erregt, sich also in Knochenschall umwandelt, daß *zweitens* bei dieser Schwingungserregung die mit den Eigenfrequenzen des Schädels übereinstimmenden Teiltöne eines Geräusches wesentlich höhere Amplituden im Schwingungsspektrum des Schädels besitzen, als die übrigen, und daß *drittens* die Wirkung von Gehörschützern doch eine recht beschränkte ist.

Um diese Folgerungen zu erhärten stülpten wir bei einigen Versuchspersonen einen aus schallabsorbierenden Material bestehenden Kopfschutz über den Schädel, sodaß mit Ausnahme des Gehörschützers der ganze Schädel umkleidet war. Dann wurde wiederum der eben beschriebene Versuch durchgeführt Die Mithörschwellen zeigten nun keine bzw. nur wenig ausgeprägte Senken (Abb 4). Durch das den Schädel umgebende schallabsorbierende Material wurde also die Umwandlung von Luftschall in Knochenschall verhindert Die Frequenzen um 3000 Hz wurden nicht mehr bevorzugt übertragen

An diesen Versuch schließt sich nun die Erwägung an, ob die für den *Lärmschaden so typische c⁵-Senke, die nach Tamura und Kushida* auch bei Benutzung von Gehörschützern auftritt, wenigstens teilweise aus dem Resonanzmaximum des Schädels erklärt werden kann Bekanntlich treten die Hauptschäden nach Tonbelastung meist in dem Schneckenbereich auf, der entsprechend einer halben Oktave näher zum ovalen Fenster liegt als dem Belastungston entspräche Das gleiche gilt auch für Schäden nach Einwirkung starker Schmalbandgeräusche Da nach unseren Untersuchungen Frequenzen um 2000–3000 Hz auch bei Luftleitung aus einem Lärmspektrum bevorzugt vom Schädel auf das Innenohr übertragen werden, ist eine Hauptschädigung bei 3000–4500 Hz zu erwarten

Weiterhin folgt aus den Versuchen, daß eine wirksame Verhinderung von Lärmschäden durch einfache Gehörschützer nicht gegeben ist, da die Frequenzen um 3000 Hz aus einem Lärmspektrum um ca 20 dB stärker auf das Innenohr übertragen werden als die übrigen Ein wirksamer Schutz gegen Lärmschaden ist nach unseren Untersuchungen nur gegeben, wenn der ganze Schädel mit schallabsorbierendem Material umkleidet ist Nur *dann tritt eine nur vom Frequenzgang des Lärmschutzes abhängige,* gleichmäßige Dämmung aller Frequenzen ein

Für wertvolle Hinweise bin ich den Herren Dr M F Wigand und Dr H G Schmitt beide HNO Klinik, Würzburg zu Dank verpflichtet

SUMMARY

The range of the main resonance frequencies of the human skull covers the region from 1200 Hz to 4000 Hz A bone conducted white noise shows therefore a

marked improvement in this region That could be verified by the pronounced masking effect of such a noise on air conducted tones in that frequency range A strong air borne white noise causes also vibrations of the skull, i e bone conducted sound, especially in the range of the main resonance frequencies of the skull It seems that this could be the reason why the normal ear protectors can not prevent an inner ear damage always

RÉSUMÉ

Les fréquences propres principales du crâne humain rangent entre 1200 Hz et 4000 Hz Un bruit blanc, transmis par conduction osseuse a un effet de masquage tout particulièrement dans cette gamme de fréquence Ceci est prouvé audiologiquement Un bruit fort transmis par l'air provoque également des vibrations du crâne L'application de couvre-oreilles normaux ne peut pas éviter la transformation du son transmis par l'air dans un son transmis par l'os Grâce aux fréquences propres du crâne ce sont surtout les fréquences entre 1200 Hz et 4000 Hz qui — faisant partie d'un bruit blanc — sont transmis à l'oreille interne On suppose que les traumatismes acoustiques qui se produisent même dans les cas où des couvres oreilles furent portés sont dus à ces phénomènes de résonance

LITERATUR

ALLEN G W und FERNANDEZ, C., 1960 The mechanism of bone conduction Ann Otol 69 5

BÁRÁNY E., 1938 A contribution to the physiology of bone conduction Acta Otolaryng (Stockh) Suppl 26

BÉKÉSY G v., 1939 Über die piezoelektrische Messung der absoluten Hörschwelle bei Knochenleitung Akust Z 4 113

— 1948 Vibration of the head in a sound field and its role in hearing by bone conduction J Acoust Soc Amer 20 749

FRANKE, L. K., 1956 a Empfänglichkeit der menschlichen Hirnschale für mechanische Schwingungen J Acoust Soc Amer 28 1277

— 1962 b zit nach Hood J Acoust Soc Amer 34 1325

HEITCHCOCK LE ROY D 1961 Clinical calibration of bone-conduction measurements Arch Otolaryng 3 186

HUIZING E H., 1960 Bone conduction The influence of the middle ear Acta Otolaryng (Stockh Suppl 1)

JAHN G., 1953 Über die Schwingungsfähigkeit des menschlichen Felsenbeines im Hinblick auf die Theorie des Knochenleitungshörens Z Laryng 32 439

JERGER, J und TILLMAN T., 1960 A new method for the clinical determination of sensorineural acuity level (SAL) Arch Otolaryng 71 948

KIRIKAE I 1959 An experimental study on the fundamental mechanism of bone conduction Acta Otolaryng (Stockh) Suppl 145

NIXON C W und GIERKE H E v., 1959 Experiments on the bone conduction threshold in a free sound field J Acoust Soc Amer 31 1121

RAINVILLE, M J 1955 Nouvelle méthode d'assourdissement pour le relévé des courbes de conduction osseuse J Franc Otolaryng 4 851

TAMURA H und KUSHIDA H., 1960 Lebensalter der Lärmarbeiter und professionelle Schwerhörigkeit Mschr Ohrenheilkunde 94 347

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THE ANATOMICAL INTERRELATIONSHIPS OF THE COCHLEAR NERVE FIBERS

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The purpose of this study was to determine the anatomical interrelationships of the dendritic and axonal fibers of the spiral ganglion. Because *irreversible neuronal degeneration* follows dendritic injury, a condition peculiar to the cochlear nerve, the method used was to create isolated *surgical lesions of the organ of Corti and* to define the related dendritic and axonal units with stains selected for degenerating fibers.

The cochlea, cochlear nerve trunk, and cochlear nuclei were removed two to six weeks after injury and treated as follows:

(1) The cochleae were *decalcified, embedded in celloidin, serially* sectioned and stained with hematoxylin and eosin.

(2) The cochlear nerve trunks were *frozen, serially sectioned and* treated with the Marchi method for degenerating nerve fibers.

(3) The cochlear nuclei were frozen, serially *sectioned, and treated* with the Nauta method for degenerating axons.

In the basal and middle turns the dendrites passed in a radial direction from the spiral ganglion to the organ of Corti but, in the apical turn, they took an angled course, rather fan like, toward the apex, suggesting that near the apex, a unit length of spiral ganglion innervated a greater area of the organ of Corti.

The apical fibers in their course from the spiral ganglion to the brain stem made about one and three-quarters turns about the axis of the nerve trunk. There was progressively less twisting for units located basalwards so that the extreme basal turn fibers entered the cochlear nerve trunk laterally and inferiorly and maintained this inferior position to the cochlear nuclei.

As has been described by others the axons entered the interstitial nucleus and bifurcated into anterior and posterior branches which entered the dorsal and ventral cochlear nuclei. The apical turn fibers ended in the most ventral part of the nuclei with the anterior branches *terminating in a* more superior *level* than the posterior. The basal turn fibers terminated more distally (deeper in the cochlear nuclei) and the anterior branches ended at a more inferior level than the posterior branches. The location of these terminations appeared to be the nuclear manifestation of the twisting phenomenon so dramatically

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displayed in the cochlear nerve trunk This twisting relationship was considered to result from the interaction of spatial and phylogenetic factors

The data from these studies has been correlated and graphically displayed in illustrations to clarify the point-to-point relationship of the dendritic and axonal endings

Previous studies on frequency localization within the cochlea make it possible now to predict the spatial distribution of frequency oriented neural units in the cochlear nerve and nuclei

INTRODUCTION

The anatomical structure of the cochlear nerve has interested many investigators. For example, Cajal (2), Lorente de No (8, 9), Streeter (25), Lewy & Kobrak (7), Fernandez (3), Bocca (1), Portmann (12), Schuknecht (19–23) and Rasmussen (13–17) have reported their anatomical, embryological, and histopathological work on the cochlea and on the cochlear nerve and nuclei

In addition, studies (5, 6, 18) of bioelectric potentials of the cochlea have provided additional information on frequency localization (19) However, despite extensive morphological data on the ultrastructural level (24), information on the neural organization of the cochlear nerve which is important to the neuroanatomist, the neurophysiologist, and the otologist is still lacking

Therefore, it will be the purpose of this study to supply information on the spatial distribution of the bipolar neurons in the cochlear nerve from the endorgan (organ of Corti) to the second order neurons (cochlear nuclei)

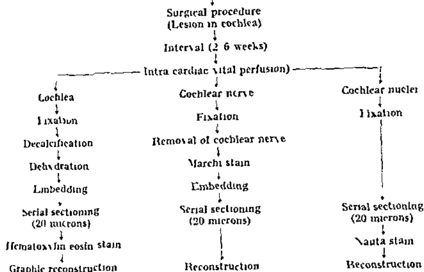
MATERIAL AND METHOD

For this study, lesions were produced in the cochleas of cats A protocol for each animal is shown in Table 1 Cochlear lesions were made while the animal was anesthetized with intaperitoneal Pentobarbital Sodium in a dosage of 50 mg per kilogram of body weight

Using an aseptic technique, the auditory bulla was opened and the bony otic capsule fenestrated with a dental burr A mechanical lesion then was made in a predetermined region of the cochlea (Fig 1) In all cases, fine needles were used and an effort was made to limit the size of the lesion to the spiral ganglion, to the dendritic nerve endings, and to the organ of Corti

After the lesion was made, the fenestration in the otic capsule was covered with a viable pedicle flap of mucous membrane from the auditory bulla, and the skin incision was closed After survival periods of from 2 to 6 weeks, the cat was again anesthetized and perfused intravitally with 500 cc of 3% Potassium dichromate in 10% Formalin The skull was opened

TABLE 1



and the cochlear nerve severed at the junction of the brain stem The entire brain stem (including the cochlear nuclei) was further fixed in 10% Formalin The cochlear nerve was removed from the internal auditory meatus with the vestibular nerve and immersion-fixed in 10% Formalin

The temporal bones were dissected from the skull, trimmed and immersed in 10% Formalin After decalcification in aqueous 5% Tri-chloro acetic acid, the specimens were dehydrated in graded alcohols over a ten-day period and then embedded in celloidin Serial sections were then cut at 20 micra in a plane parallel with the axis of the modiolus (Fig 2) Every tenth section was stained with Hematoxylin and Eosin Graphic reconstructions were made of the organ of Corti and the spiral ganglion with particular attention given to the dendritic fibers in the osseous spiral lamina as described by Schuknecht (19)

The Marchi technique as modified by Rasmussen, was used to selectively stain degenerating cochlear neurons in the cochlear nerve specimens The specimens were infiltrated with aqueous 15% gelatin and frozen cross sections of the nerve trunks (see Fig 2) were cut at 30 micra Every fifth section was employed in the reconstruction of that portion of the nerve lying within the internal auditory meatus The spatial relationship of successive sections was maintained by cutting marks into the gelatin blocks

The brain stem and cochlear nuclei were frozen sectioned in the horizontal plane (as shown in Fig 2) at a thickness of 30 micra Every fifth section was stained for axonal degeneration by Rasmussen's modified Nauta technique (1a) Reconstructions were made to trace the paths of the degenerating fibers in the interstitial, antero-ventral, postero-ventral, and dorsal subdivisions of the cochlear nuclei

Fig 1 Basal turn lesion—Cat 3

Figure 3 presents graphically the location of the lesion in the organ of Corti in the spiral ganglion and the resultant degeneration in the cochlear nerve and cochlear nuclei Barograms are used to represent the organ of Corti and the spiral ganglion with its corresponding dendritic fibers, and camera lucida drawings are used to represent the cochlear nerve and cochlear nuclei

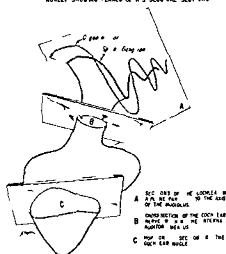


Fig 2 Lateral view of the left cochlea cochlear nerve and cochlear nuclei showing planes of histological sections

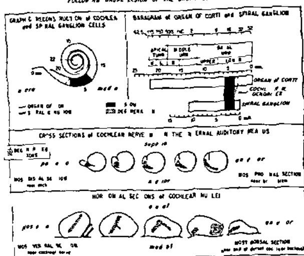


Fig 3

Since it is difficult to remove the cochlear nerve from the modiolus without damaging the cochlea, this portion of the nerve was left intact with the cochlea and was then sectioned in the plane perpendicular to the axis of the modiolus. After staining with Hematoxylin and Eosin reconstructions were made to show the location of cochlear nerve degeneration within the modiolus.

Thus in all cases the first order neurons were traced in their course from the dendritic fibers near the organ of Corti through the spiral ganglion and cochlear nerve trunk to their terminations within the cochlear nuclei.

EXPERIMENTAL RESULTS

Neuronal degeneration was produced in 21 cats following discrete cochlear lesions and 7 general categories of lesions could be defined.

Group A Lesions of the basal end of cochlea
Group B Lesions of the basal turn
Group C Lesions of the middle turn
Group D Lesions of the apical turn
Group F Combined lesions of the middle and apical turns
Group E Widespread cochlear lesions
Group G Small lesions of the organ of Corti

In 15 of these ears (Groups A F), there were discrete retrograde degenerative changes in both the cochlear nerve trunk and the cochlear nuclei. The findings in the various groups are displayed diagrammatically in Figs 4, 6, 10, 12, 14 and 17.

Fig. 1. Basal turn lesion—Cat 3

Figure 3 presents graphically the location of the lesion in the organ of Corti in the spiral ganglion and the resultant degeneration in the cochlear nerve and cochlear nuclei. Barograms are used to represent the organ of Corti and the spiral ganglion with its corresponding dendritic fibers, and camera lucida drawings are used to represent the cochlear nerve and cochlear nuclei.

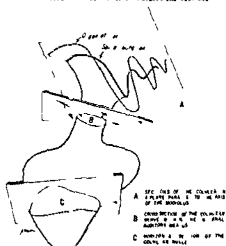


Fig. 2. Lateral view of the left cochlea, cochlear nerve, and cochlear nuclei showing planes of histological sections.



F 5 *Cochlear nerve degeneration in the nerve trunk (Hook lesion—Cat 1)*

fibers and the organ of Corti with some secondary neural degeneration at the margins of the induced lesions. Degenerated fibers could be traced from Rosenthal's canal through the osseous lamina to the foramina nervosa.

Degenerating fibers were sharply localized in distal sections appearing in the lateral inferior areas of the cochlear nerve trunk adjacent to the

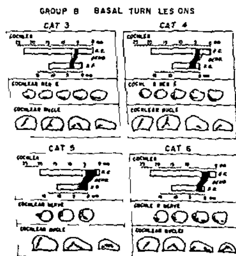


Fig. 6

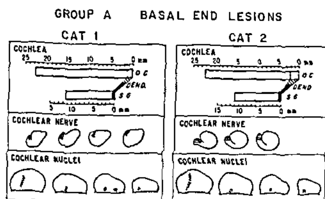


Fig 4

Group A Basal end lesions (Fig 4)

In these 2 cases the surgical approach was made through the round window and successful lesions were produced near the end of the basal turn. In each instance the spiral ganglion and its associated dendritic fibers were directly involved, but the organ of Corti itself was spared Some dendritic degeneration was noted at the periphery of the lesion, and the paths of these fibers could be seen passing toward the basal end of the organ of Corti as they passed within the osseous spiral lamina from Rosenthal's canal to the foramina nervosa, where the nerve enters the organ of Corti Histological examination of these 2 cochleae revealed unsuspected labyrinthitis which had caused widespread destruction of the organ of Corti, but this degeneration had not created neural degeneration at the time the animals were sacrificed In each cat neural degeneration occurred central to the induced cochlear lesion Marchi staining revealed the presence of a localized area of degeneration in the lateral portion of the cochlear nerve *trunk in distal sections (near the cochlea) which gradually assumed a* superior-lateral position in proximal sections (near the cochlear nuclei) (Fig 5)

These degenerating fibers were traced from their point of entrance into the cochlear nuclei as they passed from the ventro-lateral to the dorso-medial areas of the interstitial nucleus In the deepest parts of this nucleus the nerve fibers divided into anterior and posterior branches The posterior branch entered the dorsal nucleus through the posterior ventral nucleus, while the anterior branch passed into the anterior-ventral nucleus These fibers coursed upwards within their respective nuclei, disappearing first in the antero-ventral nucleus and then at higher levels into the dorsal nucleus Microscopic examination revealed no traceable degeneration in the lower part of the cochlear nuclei

Group B Basal turn lesions (Fig 6)

In 4 ears the lesions were restricted to the basal turns with no damage to the hook areas Such lesions involved spiral ganglion cells, dendritic

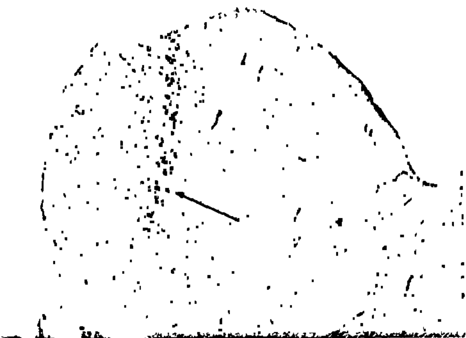


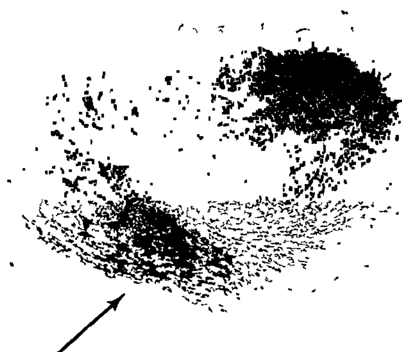
FIG 9 Cochlear nerve degeneration in the nuclei (basal turn lesion—Cat 5)

dorsally and were divided into anterior and posterior branches within the dorsal part of the interstitial nucleus, but at more ventral levels than the fibers from the basal end region of the cochlea Degenerating basal turn fibers terminated in the upper portion of the dorsal and anterior-ventral nuclei just below the neurons from the basal end region As in the case of a basal end lesion, the basal turn fibers passed to higher levels within the dorsal nucleus than in the anterior-ventral nucleus In fact, in Cats 3–6 only these fibers in the dorsal nucleus are visible Moreover, the fibers within the dorsal nucleus appeared to ascend and then turn sharply anteriorly

Group C Middle turn lesions (Fig 10)

In two cases, moderate sized lesions involved the spiral ganglion, dendritic fibers and organ of Corti of the lower middle turn Cat 7 presented greater injury to the spiral ganglion than to the organ of Corti itself, and consequently, secondary degeneration of dendrites was noted at the margins of the induced lesion These fibers were seen to pass toward the apical turn as they traversed the osseous spiral lamina from Rosenthal's canal to the foramina nervosa

Within the cochlear nerve trunk, degeneration was localized medio-superiorly in the distal sections, and gradually twisted in a clockwise direction to assume a superior position in the more medial sections Upon enter-



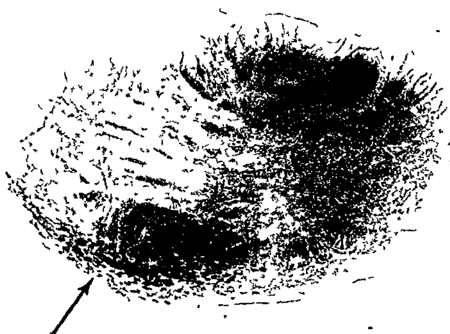


FIG. 7. Cochlear nerve degeneration in the nerve trunk (basal turn lesion—Cat 3, distal section).

FIG. 8. Cochlear nerve degeneration in the nerve trunk (basal turn lesion—Cat 3, proximal section).

fibers of the basal end region. Passing centrally, the axons spread out, appearing in sections near the brain stem as diffuse areas in the inferior portions of the nerve trunks (Figs. 7 and 8).

Within the cochlear nuclei (Fig. 9) these fibers passed medially and

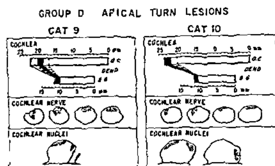


Fig 12

Group D Apical turn lesions (Fig 12)

Two cats had apical turn lesions involving the spiral ganglion, dendrites, and organ of Corti In Cat 9, the injury occurred near the apex, and secondary degeneration of dendritic filaments occurred peripherally In the other cat (Cat 10) the lesion involved the extreme apex

Studies of dendritic degeneration indicated that these fibers angle sharply toward the apex as they pass through the osseous spiral lamina on their way from Rosenthal's canal to the foramina nervosa Within the distal portion of the cochlear nerve trunk, degeneration of apical turn fibers was limited to a small central portion of the superior quadrant Proximally, the fibers moved clockwise and separated slightly, while in the glial zone they were more diffusely scattered at the superior surface of the nerve (Cats 9-10 Nerve) In Cat 9, where the lesion spared the apex of the cochlea, areas of normal fibers bounded inferiorly and medially by degenerating

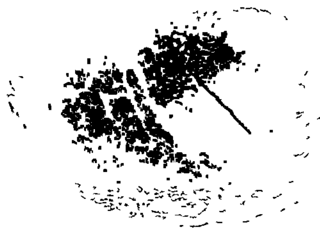


Fig 13 Cochlear nerve degeneration in the nerve trunk (apical turn lesion—Cat 9)

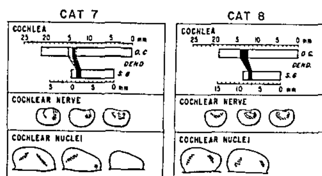


Fig. 10.

ing the glial zone of the nerve trunk, the fibers became moderately scattered, although still limited to the superior quadrant

From their point of entrance into the cochlear nuclei the middle turn fibers passed dorsally for a short distance before separating into anterior and posterior branches at a point considerably ventral and lateral to the bifurcation of fibers from the basal turn region (Fig 11). Two cases with middle turn lesions showed the posterior branch within the dorsal nucleus disappearing at a relatively higher level than the anterior branch within the anterior-ventral nucleus The posterior fibers also curved within the dorsal nucleus, but not as much as noted in cases with basal turn lesions



Fig 11 Cochlear nerve degeneration in the nuclei (middle turn lesion—Cat 7)

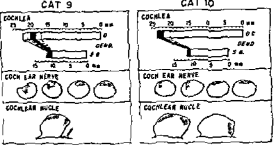


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Group D Apical turn lesions (Fig. 12)

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Studies of dendritic degeneration indicated that these fibers angle sharply toward the apex as they pass through the osseous spiral lamina on their way from Rosenthal's canal to the foramina nervosa. Within the distal portion of the cochlear nerve trunk degeneration of apical turn fibers was limited to a small central portion of the superior quadrant. Proximally the fibers moved clockwise and separated slightly while in the glial zone they were more diffusely scattered at the superior surface of the nerve (Cats 9-10 Nerve). In Cat 9 where the lesion spared the apex of the cochlea, areas of normal fibers bounded inferiorly and medially by degenerating



Fig. 13 Cochlear nerve degeneration in the nerve trunk (apical turn lesion—Cat 9

apical fibers were seen in the supero-lateral portion of the nerve trunk. In more proximal sections, these normal fibers shifted their position clockwise and superiorly (Fig 13)

Almost immediately after entering the cochlear nuclei, the degenerating fibers separated, in the most ventral areas of the interstitial nucleus, into anterior and posterior branches. As in the other cases, the anterior and posterior branches were within the anterior-ventral and dorsal nuclei respectively, but the anterior branch passed to a more dorsal level than did the posterior branch.

Group E: Combined lesions of the middle and apical turns (Fig 14)

In 2 cases, separate and distinct lesions were produced in both the apical and the upper half of the middle turns. One cat (Cat 11) showed primary involvement of the spiral ganglion, dendritic fibers, and organ of Corti while the other (Cat 12) showed primary damage to the organ of Corti and the dendritic fibers with retrograde degeneration of the spiral ganglion cells. As can be seen in the baragraphs (Cats 11 and 12, Cochlea) small lesions of the spiral ganglion, near the apex, were associated with relatively extensive lesions of the organ of Corti. Dendritic fibers angled sharply toward the apex as they passed through the osseous lamina from Rosenthal's canal to the foramina nervosa.

The cochlear nerve trunks of both cats showed two separate areas of degeneration in distal sections and in moderately proximal sections (Figs 15 and 16). Degeneration occurred in the same areas as in the cases with isolated apical and middle turn lesions. Proximally, the 2 separate areas of degeneration merged in the glial zone of the nerve trunk.

Horizontal sections through the cochlear nuclei showed 4 separate paths of degeneration with both anterior and posterior tracts terminating at levels comparable to those observed following isolated lesions of the middle and apical turns.

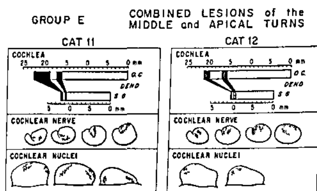


Fig 14

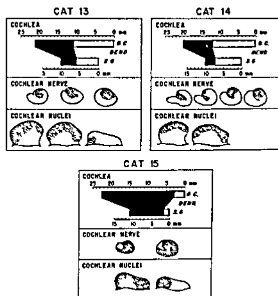


Fig 17

Group F Widespread lesions (Fig 17)

Three ears presented widespread cochlear lesions involving the spiral ganglion, the dendritic fibers, and the organ of Corti In 2 cases the primary destruction included the entire apical and middle turns (Cats 13 and 14), and in the third, only the extreme end of the basal turn escaped damage (Cat 15)

The localization of degenerated and of normal fibers within the cochlear nerve trunks and the cochlear nuclei agreed closely with predicted results from the study of previous lesions

Group G Small lesions of the organ of Corti

In 5 cats, small lesions were made in the hook region of the cochlea by passing a fine needle through the round window These lesions involved only the area of the organ of Corti There were no direct injuries to the spiral ganglia No degeneration could be found in either the nerve trunks in the internal acoustic meatus or the brain stems However, there were spotty losses of ganglion cells and dendritic fibers in 4 ears (Cats 17–19) sacrificed 3 to 5 weeks postoperatively

DISCUSSION

Retrograde Degeneration

In order to obtain, most accurately, the data on point to point projections from small areas of the organ of Corti in the different cochlear turns it was desirable to produce very small lesions in either the spiral ganglion or the dendritic process (radial fibers) of the first order neuron Thus small numbers of neurons were involved in most lesions Relationships between

the amount of end organ innervated and its representation in the cochlear nerve and nucleus were then easily deduced

Lesions involving the spiral ganglion itself produced Wallerian degeneration which was optimally demonstrated by the Marchi method after degeneration periods of about 10 days to 2 weeks Both the axons and the *myelinated dendrites of the involved* cells were utilized to map the course of these lesions

When lesions involved only the dendrites of the bipolar spiral ganglion neurons retrograde degeneration of the entire cochlear neuron ensued which could be demonstrated histologically after 3 to 4 weeks survival This bipolar neuron consistently degenerates completely when either the axon or the dendrite is injured even when the injury occurred at great distances from the cell body

Survival times therefore ranged from 2 weeks to 6 weeks depending on what type of lesion (ganglion or dendrite) was produced at the time of surgery

In some animals the lesions were restricted to the organ of Corti only Here the neural degeneration (retrograde) was noted to proceed only from those areas of the end organ where supporting elements had been lost (e g Deiter s and Pillar cells) but not from those areas of hair cell loss only (Cat 10) This pattern supports the contentions of Fernandez (3) Portman 12) and Schuknecht (22) that retrograde degeneration of the cochlear neuron after end organ lesions occurs only when the injury has been severe enough to produce loss of supporting elements

Dendritic Fibers Within the Osseous Lamina

Careful attention was paid to the radial course of dendritic fibers within the osseous spiral lamina from Rosenthal s canal to the foramina *nervosa*

In most of the basal turn these dendritic fibers run radially from spiral ganglion cells in the middle turn they are slanted slightly toward the apex and in the apical turn they become more sharply angled toward the apex until in the uppermost regions they assume a nearly *tangential* course to Rosenthal s canal (Fig 18) This is in agreement with Bocca (1) who reported a similar finding in rat fetuses

In addition at the very end of the basal turn the fibers slant slightly in the opposite direction that is toward the termination of the organ of Corti within the vestibular caecum

With the exception of the upper apical turn *where there* was a marked spreading and fanning the dendritic fibers displayed little tendency to diffuse or to scatter as they passed through the osseous lamina toward the foramina nervosa (Fig 18)

This fan shaped spreading of fibers when considered with the diagonal course of *dendritic fibers in the apical turn* suggests that in these areas a given unit length of spiral ganglion may innervate a relatively greater length

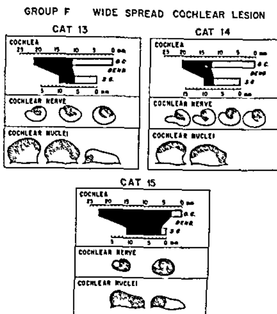


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were located inferior and medial to the apical and middle turn fibers for the entire length of the nerve. The fibers from the lower one third of the basal turn were located inferiorly but lateral to the upper basal fibers. Although there was no twisting of the fibers from the first third of the basal turn in the nerve trunk at the internal auditory meatus there was a spreading out of those fibers in shape of an arc at the proximal side of the nerve trunk. These fibers were covered inferiorly and medially by some of the twisting fibers coming from the upper two thirds of the basal turn. Although the hook region of the cochlea during embryological development twists in an opposite direction to the rest of the cochlea no similar twisting of the fibers (axon) from the hook region could be observed.

The Course of the Fibers Within the Cochlear Nuclei

Lorente de No (8, 9) (1933) reported that fibers from different cochlear turns bifurcate in an orderly dorso-ventral sequence in the interstitial nucleus. He originally reported that fibers from the apical turn bifurcate in the deepest part of the interstitial nucleus while those from the basal turn bifurcate more distally.

The findings of Lewy and Kobrak (7) demonstrated however that the opposite is true. Lorente de No also reported that if the nerve is followed from the point of division of its fibers in the interstitial nucleus toward the spiral ganglion it is found that it twists progressively as it advances each bundle of fibers turns on the axis of the nerve in the same direction as the spiral of the cochlea.

Rasmussen (14, 15) used a modified Nauta technique and demonstrated the pathway of degenerated fibers from each cochlear turn to the cochlear nuclei. His findings are in agreement with those of Lewy & Kobrak.

The concepts of Lewy & Kobrak (7) and of Rasmussen (14) are confirmed in this study that is fibers from the basal coil bifurcate and distribute most dorsomedially while those from the apical turn bifurcate and distribute most ventro laterally.

Moreover the present study reveals that the posterior branches from the apical turn axons terminate at a more inferior level in the dorsal cochlear nucleus than do the anterior branches in their terminations in the anterior ventral nucleus. In contrast the nerve terminations of the posterior branches of the basal end fibers end at a more superior level in the dorsal nucleus than do the anterior branches in the anterior ventral nucleus; the anterior and posterior branches of the middle turn axons end at about the same level. This twisting of points of termination of fibers within the cochlear nuclei may be related to embryological development of the cochlear nuclei as is the twisting of the nerve fibers within the nerve trunk. Since it has been shown that the most ventral part of the nuclei corresponds to the apical turn of the cochlea and the most apical end's fibers twist almost one and three quarters turns in the internal auditory meatus and cochlear

of the organ of Corti This effect is more pronounced near the upper, rather than the lower, apical turn

In this way a longer organ of Corti consisting *of 3 turns and a large* hook region is reconciled with a smaller spiral ganglion consisting of only $2\,^1/_2$ turns and a reduced hook

The question of distortion of results by any efferent fibers (olivocochlear bundle) as they course among the radial fibers on their way to the organ of Corti can be answered simply The ratio of efferent to afferent cochlear fibers is so small as to be negligible in this type of study

The Course of the Cochlear Nerve (Axon) in the Modiolus and Internal Auditory Meatus

Lorente de No (8) in 1933 published his careful and systematic study concerning the anatomy and embryology of the cochlear nerve Using Golgi's, Cajal's, and Weigert-Kulschitzk's *method,* he showed in mice and cats that the cochlea develops as a process of the auditory vesicle when ganglionic cells migrate to the medial side and the central processes develop and enter the medulla where they divide into 2 branches and establish connections with the nuclei before the organ of Corti develops When the organ of Corti begins to appear, the dendritic fibers connect the organ of Corti with the ganglion cells and finally become twisted In addition, he also reported that the development of the cochlea takes place not only *towards the apex, but also slightly towards the base Thus* the point of the cochlea that shows no twisting corresponds to the first third of the basal turn, the fibers innervating it constitute the axis of the cochlear nerve The fibers innervating the basal end are twisted in the opposite direction and those innervating the apical part in the same direction, as the cochlea After making lesions limited to relatively large areas of the spiral ganglion in each turn, Rasmussen (17) observed degeneration of nerve fibers in the nerve trunk by using the Marchi technique on the nerve within the internal auditory meatus *and found the localization of the nerve* fibers from each turn of the cochlea within the nerve trunk

In the present study it was assumed that Wallerian and retrograde degeneration of the cochlear nerve (afferent) could be accurately traced into the cochlear nuclei following a lesion in the cochlea Figure 18 shows the relationship between each turn of the cochlea and its associated nerves in the nerve trunk It is interesting to note that at the most proximal portion of the nerve trunk which was near the glia zone (but still within the Schwann's zone), the nerve fibers from the most apical end of the cochlea were located superiorly as shown in Fig 18 4 These fibers rotate counter clockwise 360 degrees to be located again superiorly in the distal portion of the nerve trunk *The apical turn fibers twist about three* quarters of a turn from here to their respective spiral ganglion cells

The fibers from the upper two-thirds of the basal turn of the cochlea

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modiolus, while the number of turns of spiral ganglion is approximately two and a half, there must be twisting of the nerve fibers in the cochlear nuclei. This would mean that the axis of the points of axonal bifurcation in the interstitial nucleus instead of being on a longitudinal plane would also be twisted about three-quarters turn from its most dorsal point on the axis of the interstitial nucleus.

A detailed schematic drawing has been made showing the spatial distribution of cochlear nerve fibers and the frequency localization in the cat's cochlea as described by Schuknecht (Fig 18).

ACKNOWLEDGMENTS

I am deeply grateful to Dr. Harold F. Schuknecht for assisting in the design of the experiment and with the preparation of the manuscript, to Dr Richard R Gacek for instruction in the use of nerve fiber stains and interpretation of results, and to Miss Edith Tagrin for preparation of the graphs and drawings

RÉSUMÉ

On tâchait a determiner les relations reciproques des fibres dendritiques et axonales du neurone cochleaire On pratiquait des lésions insignifiantes dans l'organe de Corti et on traçait les voies anatomiques des fibres nerveuses servant la region jusqu'a leur terminaisons dans les noyaux cochleaires, dorsal et ventral Le limaçon, les troncs nerveux cochléaires et noyaux cochleaires furent prepares et separes, avec des coupes en serie suivi de reconstruction, pour determiner leur relations dans l'espace Les fibres venant de l'apex du limaçon executent approximativement 1 3/4 torsions autour de l'axe du tronc du nerf, on observe progressivement moins de torsion dans les unites, en descendant, de la façon que les fibres les plus basales entrent dans le tronc cochleaire en bas et maintiennent cette position inférieure dans toute leur route jusqu'aux noyaux cochléaires Les fibres apicales se terminent dans la partie la plus latérale des noyaux, les fibres basales se trouvent plus eloignees Grace a la localisation des frequences dans le limaçon il est maintenant possible de predeterminer la localite des unites nerveuses orientees selon les frequences, dans le nerf et les noyaux cochléaires

ZUSAMMENFASSUNG

Die gegenseitigen anatomischen Beziehungen der dendritischen und axonalen Fasern des Schneckenneurons wurden untersucht Durch geringfugige Verletzung des Cortischen Organs wurden die anatomischen Bahnen der Nervenfasern, die diese Abschnitte versorgen, bis in ihre Endungen in den dorsalen und ventralen Schneckenkernen verfolgt Schnecke, Stamm des Schneckennerven und Schneckenkerne wurden einzeln prapariert, in Schnittserien zerlegt und mittels Rekonstruktion untersucht, um raumliche Beziehungen festzulegen Die Fasern der Schneckenspitze fuhren ungefahr 1 3/4 Drehungen um die Achse des Nervenstammes aus gegen die Schneckenbasis zu weisen die Einheiten immer geringfugigere Drehungen auf, auf diese Art treten die Fasern der extrem-basalen Windung als tiefste in den Schneckennerv ein und behalten diese tiefe Lage auf der ganzen

Strecke bis zu den Schneckenkernen Die Fasern der Spitzenwindung enden in den Kernen am weitesten seitwarts, die Fasern der basalen Windung mehr distal — Da die Frequenzlokalisation innerhalb der Schnecke bekannt ist, ist es nun moglich, die Verteilung der frequenzgerichteten Einheiten im Schneckennerven und seinen Kernen im voraus zu bestimmen

REFERENCES

1 Bocca E., 1952 Note on the innervation of the cochlea *Arch Otolaryng (Chic)* 55 188

2 Cajal, R *Histologie du systeme nerveux* I 774–838

3 Fernandez C., 1951 The innervation of the cochlea *Laryngoscope 61* 1152

4 Galek R R., and Rasmussen G L., 1961 Fiber analysis of the statoacoustic nerve of the guinea pig, cat and monkey *Anat Rec 139* 455

5 Katsuki Y., Suga N., and Kanno Y., 1962 Neural mechanism of the peripheral and central auditory system in the monkey *J Acoust Soc Amer*, 34 1396

6 Kiang N Y., and Watanabe T., 1962 Stimulus coding in the cat's auditory nerve *Ann Otol 71* 1009

7 Lewy F H., and Kobrak H., 1936 The neural projection of the cochlear spirals on the primary acoustic centers *Arch Neurol Psych* 35 839

8 Lorente de No R., 1933 Anatomy of the eighth nerve The central projection of the nerve endings of the internal ear *Laryngoscope 43* 1

9 — 1933 Anatomy of the eighth nerve General plan of structure of the primary cochlear nuclei *Laryngoscope 43* 327

10 McClung R J Marchi s Method *McClung s Handbook of Microscopical Technique* p 382

11 Nauta W J H., and Gygax P A., 1951 Silver impregnation of degenerating axon terminals in the central nervous system *Stain Tech 26* 5

12 Portmann M., and Portmann Cl., 1954 Efferent fibers of the cochlea *Arch Otolaryng (Chic)* 59 543

13 Rasmussen G L 1946 The olivary peduncle and other fiber projections of the superior olivary complex *J Comp Neurol*, 84 141

14 — Anatomical model at the symposium on the neural mechanisms of the auditory and vestibular systems June 11 13 1959 Bethesda Maryland

15 — Nauta Technique modified by G L Rasmussen and F P McCrane Laboratory of Neuroanatomical Sciences National Institute of Health July, 1960

16 1960 Efferent fibers of the cochlear nerve and cochlear nucleus *Neural Mechanisms of the Auditory and Vestibular Systems* (ed G L Rasmussen and W F Windle) chapter 8 Charles Thomas Publishers, Springfield

17 1963 Personal data

18 Rose, J., Galambos, R., and Hughes, J., 1962 Organization of frequency sensitive neurons in the cochlear nuclear complex of the cat *Neural Mechanisms of the Auditory and Vestibular Systems* (ed G L Rasmussen and W F Windle), chapter 9 Charles Thomas, Publishers, Springfield

19 Schuknecht H F., 1953 Techniques for the study of cochlear function and pathology in experimental animals *Arch Otolaryng (Chic)*, 58 377

20 1953 Lesions of the organ of Corti *Trans Amer Acad Ophthal Otolaryng*., May June 366

21 Schuknecht H F., and Woellner, R., 1955 An experimental and clinical study of deafness from lesions of the cochlear nerve *J Laryng*., 69, 75

22 — 1956 Deafness and vertigo from head injury *Arch Otolaryng (Chic)*, 63 513

23 1960 Neuroanatomical correlates of auditory sensitivity and pitch discrimination in the cat *Neural Mechanisms of the Auditory and Vestibular Systems* (ed G L

Rasmussen and W. F. Windle), chapter 6. Charles Thomas Publishers, Springfield.

24. SPOENDLIN, H. H., and GACEK, R. R., 1963: Electronmicroscopic study of the efferent and afferent innervation of the organ of Corti in the cat. *Ann. Otol.* 72: 660.

25. STREETER, G. L., 1906: The development of the membranous labyrinth and the acoustic and facial nerve in the human embryo. *Amer. J. Anat.*, 6: 139.

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COCHLEAR OXYGEN TENSION

Relation to Blood Flow and Function

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In the normal animal administration of 100% oxygen, 8% CO2 or IV epinephrine produced increases in perilymph oxygen tension. This value was highest for pure oxygen. Only CO2 or IV epinephrine increased strial blood flow rate and though similar in degree, perilymph oxygen was greater with CO2 than with epinephrine. With cessation of respiration the oxygen dissolved in the perilymph is exhausted in about 30 seconds. Surgical occlusion of the vena aqueductus cochleae results in a drop in perilymph oxygen tension to about 30% of normal along with a marked (90%) reduction in strial flow rate and about a 65% reduction in microphonic output. These low values could be raised particularly with IV epinephrine. The reasons for these findings are discussed.

The widely used polarographic method for measuring local tissue oxygen tension introduced by Davies & Brink (1942) has given relative and absolute values for oxygen in many tissues and defined conditions affecting these values. Along with other appropriate experimental methods important interrelations between local oxygen tension, blood flow, oxygen utilization, substrate (i.e. glucose) utilization, cell and organ function can now be studied. They are being actively examined in many organs, i.e. brain, heart, kidney, muscle, eye, etc. In the ear the relations between cochlear function, i.e. microphonics, action potential and cochlear oxygen tension have been reported by Misrahy *et al.* (1958) and by Koide *et al.* (1958). Direct measurements of cochlear blood flow were not made.

Relations between cochlear blood flow and function have been studied in our laboratory. The effect on the cochlear microphonics of increasing blood flow rate in the normal cochlea and in the cochlea with reduced flow due to vein obstruction were recently reported by us (Perlman *et al.* 1963, Tsunoo & Perlman 1964). In the first condition no effect was obtained while in the case of markedly reduced blood flow definite improvement in

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cochlear function paralleled increases in flow rate *in the spiral capillaries*. The explanation of these findings involved consideration of the interrelations between blood flow rate and available oxygen in the cochlea. To throw more light on this relation, a polarographic method was used to record continuously the oxygen tension in the perilymph.

METHOD

The direct moving picture recording and analysis of blood flow in the vessels of the stria vascularis and spiral ligament together with simultaneous recording of cochlear function, microphonic response to a continuous non-overloading acoustic stimulus (277 cycles at 80 db), have been described in earlier reports.

The oxygen electrode was made of a platinum wire 73 μ in diameter insulated with about 10 coats of Hysol, each coat baked at 200°C for 10 minutes. With proper dilution of the insulating material, small beads could be developed in the coating. These were useful in sealing the holes in the cochlear capsule and maintaining the position of the electrode tip in the perilymph. The reference electrode was a freshly chlorided insulated silver wire, 100 μ in diameter. Before using the oxygen electrode, a fresh platinum surface was made by cutting and the performance of the electrodes, polarized at .6 volt in a saline solution saturated in turn with oxygen, air and nitrogen, was observed. The oxygen cathode was then inserted through a hole in the cochlear capsule into the perilymph of the scala vestibuli of the basal turn and the reference electrode was inserted through a separate hole into the perilymph of the scala tympani at this level. The performance of the electrode was again checked, i.e. plateau formation with changing polarizing voltage, current output with oxygen and with air each delivered for at least 5 minutes through the respirator. At the end of the experiment a zero oxygen level was obtained with the animal breathing nitrogen through cessation of cardiac activity. The Hysol coated platinum electrode had the advantage of being flexible, easy to manipulate in a small field and could be fixed in place by cementing the wire to the edge of the bulla in a manner similar to that used for fixing the electrode wire used for detecting the microphonic potentials.

A successfully operated animal for conducting an experiment had the following: (1) A fenestra in the apical turn showing normal blood flow in the stria and spiral ligament vessels, (2) electrodes for microphonic potentials in the scala tympani and scala vestibuli of the 3rd turn, (3) electrodes in the scala vestibuli and scala tympani of the basal turn for recording oxygen tension in the perilymph, (4) cannula in the common carotid for recording blood pressure, (5) cannula in the external jugular for delivery of drugs, (6) cannula in the trachea for artificial respiration, recording of respiratory pressures and end expired CO_2, (7) needle electrodes in axilla for recording the EkG, (8) after normal recordings, a successful

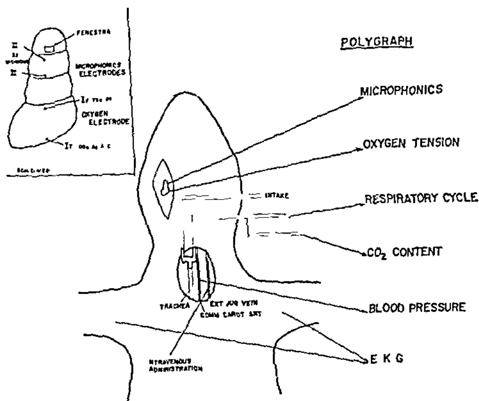


Fig 1 Schematic representation of the surgical field and connections for recording Insert shows details of cochlear field

surgical occlusion of the vena aqueductus cochleae as evidenced by markedly reduced blood flow in the vessels exposed by the fenestrum (see Fig 1)

Anoxia was produced by stopping the respirator or by administration of nitrogen at the intake of the respirator Pure oxygen and 8% CO_2 in air was delivered in a similar manner Blood pressure and cochlear blood flow were raised by continuous intravenous infusion of epinephrine Simultaneous continuous recordings of cochlear oxygen tension cochlear microphonic output blood pressure respiratory pressure carbon dioxide in end expired air and the electrocardiogram were made on a Grass polygraph Moving picture recordings of cochlear blood flow in the vessels exposed by the fenestrum were made at appropriate intervals to permit correlation with cochlear oxygen tension and cochlear microphonic output in normal and pathological states Measurements of blood flow velocity were carried out subsequently with a special projector Flow rates were measured only in the stria capillaries because of the previous observation that changes in these values were closely related to the changes in microphonic output in the cochlea with venous obstruction Observations were made on 33 albino guinea pigs weighing 250 to 350 grams

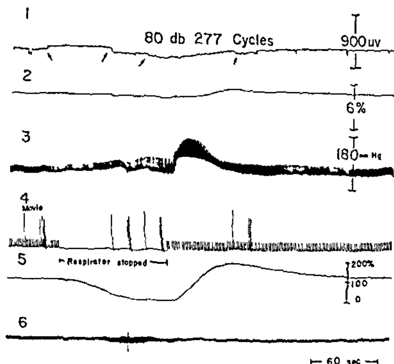
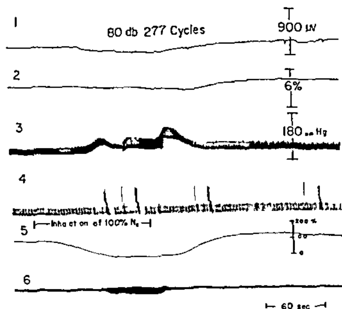


FIG. 2. Representative record of apnoea experiment. (1) microphonics from third turn, (2) CO_2 in end expired gas, (3) carotid blood pressure, (4) respiratory pressure cycle, (5) oxygen tension in perilymph of cochlea, and (6) EKG. (Arrow shows the temporary depression of microphonics due to noise while taking movie.)

RESULTS

Based on the relative current output of the oxygen electrode in air saturated saline and in the perilymph, the oxygen tension of the perilymph at the tip of the electrode appears to be very low (i.e., about 15 mm Hg). *Apnoea* (respirator off 90 seconds). Oxygen tension in the perilymph begins to fall in about 10 seconds after the respirator is stopped and precedes the drop in microphonic potential by about 10 seconds. The oxygen tension in the perilymph drops to about 60% of normal before the microphonic output shows a drop. With resumption of respiration microphonic output returns to the normal value more slowly than does the oxygen tension. Both oxygen tension and microphonic output rise at a more rapid rate than they fall at beginning of apnoea. Both the microphonic potential and the oxygen tension, particularly the latter, show a super-normal phase with recovery from apnoea. Blood flow rate during and immediately after anoxia always increased, usually two to three times normal, along with a marked rise in carotid blood pressure. There was no decrease in cochlear blood flow at any time during this short period of apnoea even when the EKG showed irregularities of the heart beat (see Figs. 2 and 3 and Table 1). *Nitrogen*. Though generally similar, some important differences in the behavior of the microphonics and oxygen tension were evident in anoxia due to 120 seconds of nitrogen breathing (see discussion).

Inhalation of 8% CO_2 in air for 5 minutes in the normal animal (artifi-



F[illegible] 3 R presentati[illegible]e rec[illegible]r[illegible] of changes [illegible]ue to anoxia fr[illegible]m inhalat[illegible]on of pure nitrogen sin[illegible] [illegible] r[illegible] [illegible] Fig 2

[illegible]ially respired) was associated with a rise in perilymph oxygen tension to 1[illegible]2% of the base line value and a rise in strial blood flow from a base rate of 101 μ/sec to 1[illegible] μ/sec The oxygen tension and blood flow remained elevated for at least 3 minutes after CO[illegible] was stopped With the animal breathing 100% oxygen a twofold increase in the oxygen tension of the perilymph was recorded with no significant change in strial blood flow rate One minute after returning to air the oxygen tension was still elevated 1[illegible]9% of normal and then it gradually dropped to the preexposure level

TABLE 1 *Changes in blood flow micr[illegible]phonics and oxygen tension caused by anoxia*

(Per cent [illegible]f normal base[illegible]ne values)

Ti[illegible]e	Anoxia: Baseline	1 m[illegible]	1½ m[illegible]	Respiration with air resumed for: 1 min	3 min
[illegible]n[illegible]					
R[illegible]spirat[illegible]r off (Apnoea)					
Bl[illegible] [illegible]fl[illegible]w	1[illegible]	3	[illegible]1	21[illegible]	9[illegible]
M[illegible]r[illegible]ph[illegible]nics	100	[illegible]	4	9	10[illegible]
Oxygen ten[illegible]	1[illegible]	[illegible]	0	151	1[illegible]
Inhalat[illegible]n [illegible]f nitr[illegible]g[illegible]n					
Bl[illegible] [illegible]fl[illegible]w	1[illegible]	181	215	1	10[illegible]
M[illegible]r[illegible]ph[illegible]n[illegible]cs	1[illegible]	[illegible]	2	8[illegible]	10[illegible]
Oxyg[illegible]n ten[illegible]i[illegible]n	10[illegible]	3[illegible]	0	3[illegible]	10

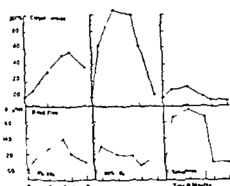
TABLE 2. *Effect of CO_2, O_2 and epinephrine on blood flow and oxygen tension*
(Changes in oxygen tension expressed in per cent of baseline value)

Time		During procedure			After stopping procedure	
	Baseline	1 min	3 min	5 min	1 min	3 min
Condition						
Inhalation of 8% CO_2 in air						
Blood flow (μ sec)	101	112	128	139	122	111
Oxygen tension	100	108	132	152	155	136
Inhalation of 100% oxygen						
Blood flow	114	131	121	110	109	119
Oxygen tension	*100*	*162*	*209*	*199*	*101*	*107*
Infusion of epinephrine (5 μg/kg/min/0.1 cc)						
Blood flow	111	166	175	166	112	111
Oxygen tension	100	109	112	99	96	96

Increases of strial blood flow from a base value of 111 μ sec to 175 μ sec were observed three minutes after onset of continuous intravenous infusion of epinephrine. Only a 12% increase in perilymph oxygen tension was recorded at this time and this returned to normal despite continuing with the infusion. The microphonic output was unchanged throughout the experiment. Some relations between cochlear blood flow and oxygen tension in the perilymph in the normal ear as influenced by 100% oxygen, 8% carbon dioxide and with I.V. epinephrine are shown in Table 2 and Fig. 4.

Marked reduction in cochlear blood flow was now produced by obstructing the inferior cochlear vein (vena aqueductus cochleae) close to the basal coil. This resulted in a stable preparation with a drop in oxygen tension to about 37% of normal, while microphonic output dropped to about 30% of normal.

Administration of 8% CO through the respirator during this state of reduced cochlear blood flow and function produced increases in cochlear oxygen tension and cochlear microphonic output and cochlear blood flow. These increases were small but definite (37 to 50% of normal for oxygen tension, 29 to 37% of normal for microphonic output, 10 to 20% of normal for blood flow). Administration of 100% oxygen raised the initial value of perilymph oxygen tension of 37% to a value of 51% of normal with a small increase in microphonic output but no change in cochlear blood flow. After 3 minutes of continuous infusion of epinephrine strial flow rate was increased from an initial depressed value of 16 μ sec to 39 μ sec along with a substantial (roughly 100%) increase in oxygen tension and microphonic output. There appears to be a close correlation between improved cochlear blood flow, cochlear micro-



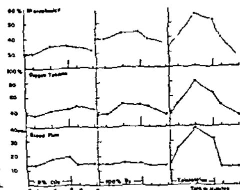


Fig 4   Fig 5

Fig 4 Graphs showing the effect of 8% carbon dioxide 100% oxygen and I V epinephrine on cochlear blood flow and oxygen tension in normal animal In Figs 4 and 5 blood flow rate in strial capillaries is given in absolute values, changes in oxygen tension and microphonic as percent of initial value

Fig 5 Graphs showing the effect of 8% carbon dioxide 100% oxygen and I V epinephrine on cochlear blood flow oxygen tension and microphonics after obstruction of the vena aqueductus cochleae

phonic output and cochlear oxygen tension produced by epinephrine after venous obstruction of the cochlea

The present increase in oxygen tension here (about 100%) is much greater than in the normal cochlea (about 12%) The effects of oxygen, carbon dioxide, and epinephrine on cochlear blood flow, cochlear oxygen tension and microphonics are shown in Fig 5 and Table 3

TABLE 3 *Effect of CO_2, O_2 and epinephrine after venous obstruction (v o)*

(Changes in microphonics and oxygen tension expressed in per cent of baseline values)

Time	Baseline Before v o	After v o	During procedure 1 min	3 min	5 min	After stopping procedure 1 min	3 min
Condition	Operation						
Inhalation of 8% CO_2 in air							
Blood flow (μ sec)	130	14	14	17	18	14	16
Microphonics	100	23	30	37	36	35	33
Oxygen tension	100	37	37	44	46	50	47
Inhalation of 100% oxygen							
Blood flow	130	16	14	15	15	13	14
Microphonics	100	40	43	44	45	40	38
Oxygen tension	100	37	38	53	51	49	36
Infusion of epinephrine (μg kg min 0 1 cc)							
Blood flow	130	16	25	33	33	13	13
Microphonics	100	35	33	56	52	41	27
Oxygen tension	100	37	50	79	61	51	37

DISCUSSION

There are many kinds of oxygen cathodes. Some (covered or recessed) are useful for measuring absolute values of oxygen tension. These electrodes respond slowly. The bare electrode on the other hand can be used for continuous recording of rapid changes in oxygen tension. Only relative changes in oxygen tension can be determined with this type. However, the bare electrode can be made very small and flexible, a particular advantage when working in the cochlea. While Misrahy (1958) and Koide (1958) each used different metals and different insulation in constructing their oxygen cathodes for intracochlear oxygen measurements, they were essentially similar to ours in that they were bare electrodes that would respond rapidly and permit continuous reading.

The amount of dissolved oxygen in the perilymphatic fluid in the immediate vicinity of the electrode is dependent on the oxygen diffusion gradient from the relatively high concentrations at the capillary (arterial and venous end) to the very low concentrations at and within the cells. The amount of this dissolved oxygen in the perilymph is also dependent on the percentage of oxygen in the gases flowing into the alveoli, the rate of oxygen delivery (blood flow rate) in the terminal vascular bed, and the rate of oxygen utilization by the cells. At least three sets of capillaries with three different diffusion pathways may provide oxygen and metabolites to the organ of Corti. However, the general statements about the strial blood flow, oxygen tension, and microphonic response would be applicable. Other factors such as the changes in the oxygen dissociation curve of hemoglobin with pH changes in the blood are also important. Artifacts due to movements of the electrode or of the fluid around the electrode must be kept in mind as well as those due to changes in temperature, protein coating or "poisoning" of the platinum surface, breaks in insulation to expose a greater active platinum surface etc. There appeared to be adequate control of these artifacts in our experiments.

In the normal cochlea stopping the respirator for 90 sec or respiring the animal with nitrogen for 120 seconds produced a drop in microphonic output, an increase in cochlear blood flow rate and a drop in cochlear oxygen tension. The brain appears to respond similarly to short periods of anoxia. According to Meyer *et al.* (1962) brief anoxia produced by stopping the respirator results in a rise in cerebral blood flow accompanied by a rise in blood pressure, a fall in brain oxygen tension (pO_2) and depression in the EEG in the monkey. Anoxia produced by apnoea is associated with carbon dioxide retention while that produced by respiring the animal with nitrogen permits CO_2 removal from the blood and alveoli. Rates of oxygen depletion are also different. In apnoea, the oxygen remaining in the alveoli is rapidly used up while with nitrogen delivered through the respirator a relatively slow replacement of the oxygen in the pump and tubing and in the animal takes place. Similarly rate differences in oxygen repletion occurs with

resumption of respiration with air. In the apnoea experiment oxygen tension dropped slowly and recovered rapidly. Increases in cochlear blood flow and decreases in oxygen tension in the perilymph were also more prompt in apnoea than in nitrogen breathing. All the increases in blood flow rate were directly measured. No new blood vessels appeared in the area exposed by the fenestrum even when anoxia was continued to cessation of blood flow due to heart failure. The initial normal value for oxygen for 10 seconds after the onset of the anoxia indicates an adequate amount available in the perilymph (scala vestibuli) for normal hair cell function and microphonic output. Normal function was maintained until the oxygen tension in the perilymph had dropped to 60% of normal. Then both the microphonic potential and cochlear oxygen tension declined smoothly. From the polarographic record it would appear that almost all the available oxygen in the perilymph was used up in about 30 seconds. This state of oxygen exhaustion was continued for another 30 seconds. This rapid exhaustion of oxygen in the perilymph indicates the high rate of oxygen utilization by the cochlea and the small amount of oxygen reserve in these fluids. The rapid exhaustion of oxygen in the perilymph, when oxygen supplies are cut off, corresponds to the findings in the endolymph by Misrahy (1958), in the cerebral cortex by Meyer (1954), and in cardiac muscle by Sayen (1958). No abrupt change was noted in these values. During the period of smooth decline of microphonic and oxygen tension a close relation would appear to exist between hair cell metabolism and amount of available oxygen below a critical value i.e. 60% of normal in the perilymph of the scala vestibuli. The exact value for oxygen tension in blood perfusing the cochlea or in the perilymph when the microphonic output began to decline was not determined. For blood perfusing the brain or skeletal muscle (above some "critical value" for minute flow) normal oxygen consumption is maintained by greater extraction of oxygen from the circulating blood and increased volume of flow. Below this "critical value" for blood flow (oxygen delivery rate) a drop in oxygen consumption follows the drop in available oxygen. At a constant flow rate, oxygen consumption declined when the oxygen tension of the arterial blood perfusing the muscle was reduced below about 60 mm Hg and of venous blood about 25 mm Hg (see Stainsby *et al.* 1964). *Hirsch et al.* (1961) also report that for the brain, 25 mm O_2 tension in venous blood is the "critical value" below which cerebral oxygen consumption drops. In the vicinity of the mitochondria of muscle cells Stainsby calculates an oxygen tension of about 5 mm Hg at this time. He points out that oxygen uptake in mitochondria is steady down to this value, thus roughly corresponding to the "critical value" measured above. Sayen *et al.* (1958) studying critical narrowing of the coronary, found that the EKG was normal until the oxygen availability (Polarographic) had declined at least 35%.

In our experiments the more rapid return of oxygen values on termination of apnoea over termination of "nitrogen breathing" may be partly explained by the markedly increased blood flow rate at this time (271%

normal) which leads to greater rate of oxygen diffusing to the electrode. The increased flow rate may also account for the supernormal period when oxygen tension, 1 min after resumption of respiration, reaches 150% of normal. On resumption of respiration the flow rate returned to normal in 3 minutes while oxygen tension was still elevated (124% of normal). With anoxia produced by 120 seconds of nitrogen breathing there is a similar increase in cochlear blood flow rate with elevated carotid pressure. The oxygen tension of the perilymph drops to the zero level in about 90 seconds, then with air in the respirator, the oxygen tension slowly returns to normal in 3 minutes with a less marked supernormal period. After 1 minute the *cochlear oxygen tension* is only 36% of normal when *strial blood flow* is still elevated (175% normal). This difference in recovery rate of oxygen tension in perilymph with nitrogen breathing may be due to the relatively slow wash out of nitrogen from the respirator and alveoli. At the peak of blood flow, oxygen in the alveoli and blood was probably still very low. While at 3 minutes when the flow had returned to normal, oxygen in the blood and alveoli was probably close to normal. Meyer (1962) *et al.* reports that in the cortex oxygen tension levels of about 10 mm Hg produced cation flux and slowing of the EEG while with cortical O_2 tension levels of 6 mm Hg the EEG became flat. Sayen *et al.* state that the ischaemic myocardium can use up all the available oxygen in 30 sec while the overshoot of oxygen tension in the myocardium recorded polarographically on release of coronary obstruction is probably due to increased coronary blood flow. Increased blood flow in the coronary under similar conditions was measured by Coffman & Gregg (1961) in a study of oxygen debt repayment after myocardial ischaemia.

The increase in cochlear oxygen tension and cochlear blood flow produced by respiring the guinea pig with 8% CO_2 in air resembles that found in endolymph by Misrahy *et al.* (1958), in cisterna fluid by Floor *et al.* (1961) and in cerebral cortex by Meyer *et al.* (1962). In addition to the importance of elevated blood flow rate in determining greater polarographic values in hypercarbia Meyer points out that the Bohr effect may be a factor. With acidosis produced by breathing 8% CO_2 as in apnoea more oxygen becomes available because dissocation of oxygen from hemoglobin is facilitated. Cross & Silver (1962) believed that the increases in cerebral oxygen tension (pO_2) after breathing 9% CO_2 mixtures were largely due to increases in cerebral capillary blood flow in their animals although decrease in O_2 utilization by the brain cells was also considered since high concentrations (30%) of CO_2 can produce anesthesia. Inhalation of 100% oxygen promptly increases the oxygen in perilymph to double the normal value corresponding to the findings of Misrahy *et al.* (1958) in endolymph. However, our measurements showed no change in cochlear blood flow rate at this time. According to Reivich (1964) controlled changes in cerebral blood flow rate from about 20 to 100 cc/min/100 gram of brain produced with controlled changes in pCO_2 were not affected by changes in blood pO_2 between 60 and 380 mm

Hg. Hence, a wide range of blood pO_2 values appear to be compatible with a constant cerebral blood flow. The perfusion pressure was maintained within narrow limits during the experiments on cerebral blood flow in the monkey by Reivich. Lambertsen (1961) found that an arterial pO_2 above 50 mm Hg had no effect on cerebral blood flow in man.

In man, Kety (1953) found only a small (13%) decrease in cerebral blood flow with inhalation of 100% oxygen. With administration of epinephrine the normal cochlear blood flow rate could be elevated even more than with 8% CO_2 but the oxygen tension in the perilymph was only minimally changed. Cross & Silver (1962) found relatively small brief elevations of forebrain oxygen tension with injection of 3 μg of epinephrine in the rabbit. Clark *et al.* (1958) report that in the awake cat with chronically implanted oxygen electrodes, the mean cerebral oxygen tension is not altered by most vasoconstrictor or vasodilator drugs, i.e., injection of epinephrine 2 mg/kg intramuscular. They found that the only substances that consistently increased cerebral pO_2 were carbon dioxide, oxygen and ether. It is not clear why elevated cochlear blood flow in the normal cochlea due to CO_2 is associated with marked increase in perilymph oxygen tension while equally elevated cochlear blood flow rate with epinephrine *produces only* a minimal rise in cochlear oxygen tension. Perhaps the Bohr effect (increased oxygen dissociation of hemoglobin) in CO_2 breathing is the important difference. It may also account for the supernormal pO_2 on recovery from apnoea in association with increased cochlear blood flow rate.

Venous obstruction of the cochlea

Marked reduction in cochlear blood flow rate to about 10% of the normal value along with a dilation of the strial capillaries could be produced by occlusion of the vena aqueductus cochleae. At this time, due to the increased venous pressure the blood volume of the capillary bed was roughly doubled by dilation of the vessels so that the overall oxygen delivery rate was reduced to about 20% of normal. The reduced oxygen delivery rate *to the* end organ even with maximum oxygen extraction is now *apparently unable* to *provide* for normal cochlear microphonic output. However, *a reduced* microphonic output could be sustained for several hours, probably the expression of reduced metabolism of the hair cells as a result of *reduced* oxygen supply. The experiments of Chance *et al.* (1962) *indicate that when* the normal intracellular oxygen tension of about 1 mm Hg *is reduced to* 2 mm Hg, cell respiration (reduction of pyridine nucleotide) *drops to about* 50% of normal. With smaller reduction in *cochlear blood flow* rate (80% of normal) due to improperly placed *occlusions of the* vein, no change in oxygen tension or microphonics was *noted*. *Hirsch* (1957) found that oxygen uptake of the *brain begins to drop* when cerebral blood flow is 50% of normal. Fales (1962) *reports that* in reduced *blood flow* in muscle due to partial venous occlusion, oxygen consumption is reduced in proportion to blood flow and sustained low values for blood flow and oxygen

consumption could be produced by partial venous occlusion. Administration of 100% oxygen after venous obstruction, causes a smaller than normal rise in oxygen tension of the perilymph. Unlike the normal a small increase in microphonic output was now recorded probably due to the additional oxygen dissolved in the plasma and perilymph and made available to the end organ. Denny-Brown & Meyer (1957) report an improvement in the EEG at the periphery of a cerebral infarct with administration of 100% oxygen. Sayen *et al.* (1958) found that the after "critical" narrowing of the coronary artery, breathing 100% oxygen produced slight improvement in the abnormal electrocardiogram. Unlike the results with 100% oxygen administration of 8% CO_2 after venous obstruction produced increases in cochlear blood flow as well as in cochlear oxygen tension and cochlear microphonics. While the absolute values were smaller, the percent improvement was similar to that in the normal cochlea. Improvement of blood flow with administration of CO_2 is also reported in cerebral lesions. Breathing a mixture of 6% CO_2 improves cortical pO_2 and blood flow at the border of an ischaemic area resulting from occlusion of the middle cerebral artery according to Meyer & Gotoh (1961).

Administration of epinephrine after venous obstruction of the cochlea produced substantial increases in all recorded parameters (cochlear blood flow, cochlear oxygen tension and cochlear microphonics). This is unlike the findings in the normal cochlea. In both normal and venous obstructed cochleas I.V. epinephrine increases blood flow. In the normal cochlea this is accompanied by only a small increase (12%) in perilymph oxygen tension and no change in microphonic output while in the venous obstructed cochlea there was a greater percent increase in flow rate, oxygen tension and microphonics above the initial depressed value (see Fig. 5). The substantial elevation in oxygen tension and microphonics following the elevation in blood flow rate may be related to the oxygen gradient between the arterial and venous end of the capillary, between the capillary and the cells and the low absolute value for oxygen in the tissue when capillary flow is markedly reduced. Improvement in flow now reduces these gradients and raises the absolute value in the tissue as a result of increases in the rate of oxygen delivered by the blood. According to the calculations of Thews (1963) for normal rates of cerebral oxygen consumption blood must remain for 7 sec in the capillary to maintain the normal gradient of oxygen tension between the arterial (95 mm Hg) and venous end of the capillary (34 mm Hg) and a normal gradient between the venous end of the capillary (34 mm Hg) and the tissue (17 mm Hg). With markedly reduced flow rates these gradients in oxygen tension would become very steep and should respond more effectively to increases in blood flow rate. Denny-Brown & Meyer (1957) report that arterial and venous stasis following occlusion of the middle cerebral artery could be reversed by elevating systemic blood pressure with epinephrine. A corresponding rise in cerebral oxygen tension was recorded polarographically. Meyer *et al.* (1954) found that low polaro-

graphic values associated with low systemic blood pressure could be elevated by raising the blood pressure and thus raising the cerebral blood flow. These above observations indicate the importance of flow rate changes in controlling available oxygen in states of reduced blood flow. The elevation of perilymph oxygen tension to within 80% of normal with only partial restoration of microphonic output (to 55% of normal) is in contrast to the findings in acute anoxia where oxygen tension levels fell to about 60% of normal before the microphonic output (to a 277 cycle tone at 80 db) was reduced.

This difference may be due to the accumulations of metabolites, change in pH and cations after prolonged reduced flow and reduced oxygen supply in venous obstruction that could not be restored to normal during the relatively short time (5 minutes) of induced elevated blood flow. Misrahy (1958) observed that when microphonics were reduced by rapid local depletion of oxygen with glucose oxidase in the perilymph (i.e., scala tympani) recovery was slow (10–15 minutes) indicating the time needed for diffusion of new oxygen from the adjacent cochlear vessels through the perilymph to the hair cell. The role of increased perfusion rate of glucose free media in maintaining cerebral metabolism studied by Geiger (1957) suggests that high flow rates facilitate removal of toxic non-carbohydrate breakdown products of cell metabolism. The role of perfusion of the scala vestibuli with oxygen free Ringers in maintaining electrical activity also suggests the formation of toxic breakdown products in the cochlea during anoxia (Honrubia *et al.* 1962).

ZUSAMMENFASSUNG

Bei normalen Tieren nahm der perilymphatische O_2-Druck der Cochlea durch Verabreichung von 100% O_2 oder IV Epinephrin zu. Die Zunahme war am höchsten für 100% O. Die Zunahme des pO_2 bei CO_2 ist grosser als bei Epinephrin mit gleicher Zunahme in Stromungsgeschwindigkeit des Blutes. Ohne O_2 Zugabe wird O_2 in der Cochlea innerhalb 30 Sekunden aufgebraucht. Die nach ven ser Okklusion speziell durch Epinephrin hervorgerufene Zunahme des Blutstroms und O_2 Drucks ist von Zunahme der Mikrophonenpotentiale begleitet. Zusammenhange dieser Befunde werden besprochen.

REFERENCES

Brown, B. M., Fricker, J., Hellis, Jr., F., Nishioka, H. and McCutchen, J., 1961. A study of cerebrospinal fluid oxygen tension. *Arch. Neurol. (Chic.)* 4, 37 4r.

Chance, B., Cohen, P., Jobsis, F. and Schoener, B., 1962. Intracellular oxidation reduction state *in vivo*. *Science* 13[illegible], 499–508.

Clark, L. C., Misrahy, G. and Fox, R. P., 1958. Chronically implanted polarographic electrodes. *J. Appl. Physiol.* 13, 85–91.

Coffman, J. D. and Gregg, D. E., 1961. Oxygen metabolism and oxygen debt repayment after myocardial ischemia. *Amer. J. Physiol.* 201, 881–887.

Davies, P. W. and Grenell, R. G., 1962. Some factors affecting oxygen tension in the brain and other organs. *Proc. Roy. Soc. Med.* 156, 483–499.

29 – 635963

DAVIES P W., and BRINK F 1942 Microelectrodes for measuring local oxygen tension in animal tissue *The Review of Scientific Instruments* 13 524 533
DENNY BROWN D and MEYER J S 1957 The cerebral collateral circulation *Neurology* 7 567 579
EALES J T HEISEY S R and ZIERLER K L 1962 Blood flow from and oxygen uptake by muscle during and after partial venous occlusion *Amer J Physiol* 203 470 474
GEIGER A 1958 Correlation of brain metabolism and function by the use of a brain perfusion method *in situ* *Physiol Rev* 38 1 20
HIRSCH H GELICHMANN A., KRISTEN H and MACAZINOVIC A 1961 Uber die Beziehung zwischen O_2 Aufnahme des Gehirns und O Druck im Sinusblut des Gehirns bei uneingeschrankter und eingeschrankter Durchblutung *Pfluegers Arch Ges Phys* 273 213-222
HONRUBIA V JOHNSTONE B M BUTLER R A., and FERNANDEZ C., 1962 Maintenance of cochlear potentials during anoxia *Fed Proc* 21 343
KETY S S 1953 Cerebral circulation Symposium on circulation and homeostasis *Medical Science Publication No 2* 180 195
KOIDE Y KONNO M and MORIMOTO M 1958 Studies on the oxigraphic measurement of the oxygen tension in the labyrinth *Ann Otol* 67 348 359
LAMBERTSEN C J., 1961 *Bard's Medical Physiology* 11th Edition C V Mosby Co., St Louis p 652
MEYER J S GOTOH F TASAKI Y HAMAGUCHI K ISHIKAWA S., NOUAILHAT F., and SYMON L 1962 Regional cerebral blood flow and metabolism *in vivo* *Arch Neurol* 560-581
MEYER J S and GOTOH F 1961 Interaction of cerebral hemodynamics and metabolism *Neurology* 11 46 65
MEYER J S FANG H C and DENNY BROWN D 1954 Polarographic study of cerebral circulation *Arch Neurol Psychiat* 72 296 312
MISRAHY G A SHINABARGER E W and ARNOLD J E., 1958 Changes in cochlear endolymphatic oxygen availability action potential and microphonics during and following asphyxia hypoxia and exposure to loud sounds *J Acoust Soc Amer* 30 701 704
MISRAHY G A HILDRETH M K SHINABARGER E W., CLARK L C and RICE A F 1958 Endolymphatic oxygen tension in the cochlea of the guinea pig *Ibid* 247 250
MISRAHY G A DE JONGE B R SHINABARGER E W and ARNOLD J E., 1958 Effects of localized hypoxia in the electrophysiological activity of the cochlea of the guinea pig *Ibid* 705 709
PERLMAN H B TSUNOO M., and SPENCE A., 1963 Cochlear blood flow and function Effect of pressor agents *Acta Otolaryng (Stockh)* 6 587 598
REIVICH M 1964 Arterial PCO and cerebral hemodynamics *Amer J Physiol* 206 25 35
SAYEN J J SHELDON W F PEIRCE G and KUO P T 1958 Polarographic O the epicardial electrocardiogram and muscle contraction in experimental acute regional ischemia of the left ventricle *Circulat Res* 6 779 798
STAINSBY W N and OTIS A B 1964 Blood flow blood oxygen tension oxygen uptake and oxygen transport in skeletal muscle *Amer J Physiol* 206 858 866
THEWS G 1963 Implications and pathology of oxygen diffusion at the capillary level *Selective Vulnerability of the Brain in Hypoxaemia* F A Davis Co., Philadelphia p 27 35
TSUNOO M and PERLMAN H B 1964 Venous obstruction of the cochlea Blood flow and function *Acta Otolaryng (Stockh)* 8 127 138

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DEVELOPMENT OF HEARING IN THE NORMAL CBA-J MOUSE

Correlation of Physiological Observations with Behavioral Responses and with Cochlear Anatomy

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In the mouse cochlear potentials appeared first with narrow ranges on the eighth day after birth and gradually increased by the fourteenth day when the responses attained adult values. Nerve action potentials as recorded from the round window appeared on the ninth day when cochlear potential ranges extended from 0.6 to 8 kc. N_1 N_2 as recorded from the eighth nerve appeared one day after the N_1 N_2 as recorded from the round window membrane. The Preyer responses appeared when action potentials could be recorded from the eighth nerve. The development anatomical changes in the mouse are similar to those found in the albino rat. The structures in the cochlea are present at birth and then there is gradual maturation of the organ of Corti, reaching adult size by the eighth to tenth day. The mature configuration of the cochlea by the tenth day correlates with the behavioral and physiological findings.

INTRODUCTION

The development of hearing varies in different laboratory animals. Larsell, McCrady & Zimmermann (1935), Larsell, McCrady & Larsell (1944) and McCrady, Wever & Bray (1940) have studied the development of physiological and behavioral responses to sound in the opossum. Wada (1923) made an extensive study of the development of the inner ear in the albino rat and correlated the findings with the Preyer reflex. Alford & Ruben (1963) studied the onset of cochlear potentials and the N_1 N_2 responses to a click in the developing mice but did not report on the development of cochlear potentials at different *frequencies*.

In the present experiments, correlation is made between the cochlear potential ranges, the behavioral responses *and the* anatomical findings in the ears of developing CBA-J mice. Also a correlation is made with the

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DAVIES P. W. and BRINK F. 1942. Microelectrodes for measuring local oxygen tension in animal tissue. *The Review of Scientific Instruments 13* 524–533
DENNY BROWN D. and MEYER J. S. 1957. The cerebral collateral circulation. *Neurology* 7 567–579
FALES J. T., HEISEY S. R. and ZIERLER K. L. 1962. Blood flow from and oxygen uptake by muscle during and after partial venous occlusion. *Amer J Physiol 203* 4 0 4 I
GLEICHER A. 1958. Correlation of brain metabolism and function by the use of a brain perfusion method in situ. *Physiol Rev 38* 1–20
HIRSCH H., GLEICHMANN A., KRISTEN H. and MAGAZINOVIC V., 1961. Über die Beziehung zwischen O Aufnahme des Gehirns and O_2 Druck im Sinusblut des Gehirns bei uneingeschränkter und eingeschränkter Durchblutung. *Pfluegers Arch Ges Physiol* 273 213 222
HONRUBIA V., JOHNSTONE B. M., BUTLER R. A. and FERNANDEZ C., 1962. Maintenance of cochlear potentials during anoxia. *Fed Proc 21* 343
KETY S. S. 1953. Cerebral circulation. Symposium on circulation and homeostasis. *Medical Science Publication No 3* 180 19 ›
KOIDE Y., KONNO M., and MORIMOTO M., 1958. Studies on the oxigraphic measurement of the oxygen tension in the labyrinth. *Ann Otol 67* 348–359
LAMBERTSEN C. J., 1961. *Bard's Medical Physiology* 11th Edition. C V Mosby C., St Louis p 652
MEYER J. S., GOTOH F., TASAKI Y., HAMAGUCHI K., ISHIKAWA S., NOUAILHAT F. and SYMON L. 1962. Regional cerebral blood flow and metabolism in vivo. *Arch Neurol* 560 581
MEYER J. S. and GOTOH F. 1961. Interaction of cerebral hemodynamics and metabolism. *Neurology 11* 46 C›
MEYER J. S., LANG H. G. and DENNY BROWN D. 1954. Polarographic study of cerebral circulation. *Arch Neurol Psychiat 72* 296 312
MISRAHY G. A., SHINABARGER E. W. and ARNOLD J. E. 1958. Changes in cochlear endolymphatic oxygen availability, action potential and microphonics during and following asphyxia, hypoxia and exposure to loud sounds. *J Acoust Soc Amer 30* 701 704
MISRAHY G. A., HILDRETH M. K., SHINABARGER E. W., CLARK L. C. and RICE A. J. 1958. Endolymphatic oxygen tension in the cochlea of the guinea pig. *Ibid* 247 2 0
MISRAHY G. A., DE JONGE B. R., SHINABARGER E. W. and ARNOLD J. E. 1958. Effects of localized hypoxia in the electrophysiological activity of the cochlea of the guinea pig. *Ibid* 705 709
PERLMAN H. B., TSUNOO M., and SPENCE A. 1963. Cochlear blood flow and function. Effect of pressor agents. *Acta Otolaryng (Stockh)* C 587 598
REIVICH M. 1964. Arterial PCO and cerebral hemodynamics. *Amer J Physiol 206* 25 35
SAYEN J. J., SHELDON W. F., PEIRCE G. and KUO P. T. 1958. Polarographic O the epicardial electrocardiogram and muscle contraction in experimental acute regional ischemia of the left ventricle. *Circulat Res* C 779 798
STAINSBY W. N. and OTIS A. B. 1964. Blood flow, blood oxygen tension, oxygen uptake and oxygen transport in skeletal muscle. *Amer J Physiol 206* 858 866
THEWS G. 1963. Implications and pathology of oxygen diffusion at the capillary level. *Selective Vulnerability of the Brain in Hypoxaemia*. F. A. Davis Co., Philadelphia p 27 3›
TSUNOO M. and PERLMAN H. B. 1964. Venous obstruction of the cochlea. Blood flow and function. *Acta Otolaryng (Stockh)* 8 127 138

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pulse of 0.07 msec was used to generate the clicks. Sound pressure levels of the pure tones were measured by a Bruel and Kjaer calibrated microphone type 4133 set parallel to the mouse's ear, and a Bruel and Kjaer wave analyzer type 2107. All db readings for the pure tones are relative to 0.0002 dynes/cm². Click intensities are relative to human thresholds.

At the end of the experiment the animal was perfused with saline and 10% formalin in a manner similar to that described by von Bekesy, Wever, Rahm & Thomas Rambo (1961). The heads were removed, trimmed and decalcified. They were imbedded in celloidin and serially sectioned at 14 micra. Each fifth section was stained with hematoxylin and eosin and mounted for study.

Observations

I. *Anatomical*

A. *External Ear.*—The external canals of the mice are closed until the eighth day. By the eighth day, a very narrow lumen can be seen. Gradually the canal opens and by the twelfth day it is fully opened.

B. *Middle Ear.*—At birth the cavity of the middle ear proper and the tympanic bulla are filled with a gelatinous embryonic tissue. This mesenchymatous tissue can still be found in the region of the round and the oval windows by the eighth day. Most of this embryonic tissue has disappeared by the ninth and tenth days.

C. *Inner Ear.* Wada studied the developmental anatomy of the labyrinth in the albino rat and made measurements of the several structures of the inner ear at various stages of development. The present study will not attempt to repeat such an anatomical description but will describe the changes qualitatively as they occur with development.

(a) *Haircells.* At birth (Fig. 1) the haircells are low columnar or cuboidal in shape, each has a basally located nucleus. The hairs can be seen coming from the upper surface. The inner haircells may be slightly longer than the outer haircells. At three days of age the outer haircells are taller and more prominent. They gradually elongate and become more cylindrical. The inner haircell becomes somewhat elongated and plump ovoid in shape. The inner and outer haircells have adult appearance and configuration by the eighth day in all turns.

The spaces of Nuel appear after the fifth day in the upper basal and lower apical portions of the cochlea. (The mouse cochlea has only two turns, basal and apical.) These spaces then continue to open first in the basal turn and extend last to the apical turn. The spaces of Nuel are complete in all turns of the cochlea by the ninth day.

(b) *Pillar cells and tunnel of Corti.* At birth (Fig. 1) the pillar cells are small, cuboidal and in contact with each other. Only a faint area between the pillar cells suggests the future site of the tunnel of Corti. This space is present in the upper basal and lower apical portions of the cochlea. The space becomes more apparent by the second and third day when the pillar

eighth nerve action potentials as *recorded* from the round window membrane (N_1 N_2), and from the *trunk of the eighth nerve* (R_1 R_2)

Mice have been chosen because certain strains carry genes of various types of degeneration of the inner ear The inner ear lesions are thought to be similar to some of those encountered in man The studies on the development of hearing in the normal mouse serve as a reference when studying hearing loss in mice with degenerative lesions of the inner ear

METHODS

Seventy-six mice from eighteen different litters were studied The mice were anesthetized with a 20% Urethane solution, using a total of 0 05 to 0 1 cc injected intraperitoneally The round window was exposed by making a hole in the lateral caudal aspect of the tympanic bulla The external auditory canal was opened near the annulus so that sound could reach the tympanic membrane without obstruction The eighth nerve was exposed by removing the calvarium over the cerebellum and aspirating the paraflocculus from the subarcuate fossa Retraction of the medulla then exposed the eighth nerve

The equipment used for recording, amplifying and calibration was as follows A ball tipped platinum wire of 0 0015" in diameter, coated with teflon, except at the tip, was used to record from the round window membrane The same electrode was used for recording action potentials from the trunk of the eighth nerve The indifferent electrode was in the neck muscles for all of the recordings

The round window electrode was connected to a Tektronix type 122 preamplifier set to record from 8 to 40,000 cycles per second The output of the preamplifier was fed into a Bruel and Kjaer wave analyzer type 2107, and the cochlear potentials were selected and measured They were also monitored on the face of the cathode ray oscilloscope For baseline comparison the amount of sound pressure needed to give a 0 5 microvolt cochlear potential was determined

The nerve action potentials picked up at the round window membrane or from the eighth nerve were amplified with a Tektronix type 122 preamplifier set to record from 8 to 1000 cycles per second The output of the preamplifier was displayed on the face of the cathode ray oscilloscope, Tektronix type 502 and the responses were photographed with a Grass camera

Experiments were carried out in an electrically shielded, soundproofed room The ears were stimulated with pure tones and clicks in a free field Pure tones were generated with a General Radio oscillator type 1304-B amplified with a McIntosh 75 watt amplifier, and attenuated with a Hewlett Packard attenuator type 350-A The output of the attenuator was fed into a Janszen electrostatic speaker The clicks were generated with a Tektronix pulse generator type 161 and wave form generator type 162 A

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(f) *Spiral ganglion and nerve fibers* At birth the spiral ganglion cells are small and irregular in size As the animal grows, the ganglion cells become larger and more uniform They assume normal size and configuration by the tenth day of age

Few nerve fibers can be seen in the osseous spiral lamina at birth with the use of light microscopy and H & E stain Gradually, more nerve fibers are seen and by the tenth day the osseous spiral lamina appears full of nerve fibers

(g) *Basilar membrane* At birth (Fig 1) the basilar membrane is narrower than that found in the adult It also appears thicker due to the presence of four to five layers of mesenchymal cells on the scala tympani side of the fibrous layer With the growth of the animal the cells diminish and the basilar membrane appears thinner Two layers of cells can still

TABLE 1 *Development of cochlear potentials in kilocycles (Kc), N_1 and N_2 and Preyer reflexes in the CBA-J mouse*

LITTERS	KK	AA	PP	II	UU	QQ	WW
Day 8							
C P Range	0 6 2	0 6–2	Absent	Absent	0 8–2	1 1 5	
N_1 N_2	Absent	Absent	Absent	Absent	Absent	Absent	
Preyer	Absent	Absent	Absent	Absent	Absent	Absent	
Day 9							
C P Range	0 6 8	0 6–8	0 6–4	0 9 2	0 8–4	0 6–8	1 4
N_1 N_2	Present	Present	Absent	Absent	Absent	Present	Absent
Preyer	Present	Absent	Absent	Absent	Absent	Absent	Absent
Day 10							
C P Range	1 20	1 8	0 6 14	2 20	0 8 10		0 8–10
N_1 N_2	Present	Present	Present	Present	Present		Present
Preyer	Present	Present	Present	Present	Present		Present

LITTERS	KK	WW	XX	LL	YY	G	I
Day 11							
C P Range	0 8 40	0 6–30	0 8 40	0 6–35	0 8 30		
N_1 N_2	Present	Present	Present	Present	Present		
Preyer	Present	Present	Present	Present	Present		
Day 12							
C P Range			1 40	1–40	1–40	1 40	1–40
N_1 N_2			Present	Present	Present	Present	Present
Preyer			Present	Present	Present	Present	Present
Day 14							
C P Range				1–40	1–40	1 40	1–40
N_1 N_2				Present	Present	Present	Present
Preyer				Present	Present	Present	Present



Fig. 1. Cochlea of newborn CBA/J mouse. M 979. Mag. ×200.

cells become taller and start to separate. On the fourth day the tunnel of Corti is definitely open and nerve fibers can be seen passing through it. The tunnel opens first in the upper basal and lower apical portions of the cochlea and gradually extends basally and then apically. By the eighth day the pillar cells have normal adult configuration and the tunnel has an adult size.

(c) *Tectorial membrane*. At birth the tectorial membrane is composed of a thick and a thin portion (Fig. 1). The thick portion extends from the limbus to the inner haircells and the thin portion extends over to the outer haircells and supporting cells. As the animal grows, the thicker portion becomes thinner and extends to the outer haircells.

At birth the space under the tectorial membrane and in between the limbus and the inner haircell is filled with numerous tall cells which have a clear cytoplasm in their upper part and basal nuclei. Atrophy of these cells begins around the fourth day and the inner sulcus space appears. As the animal grows the sulcus cells diminish to a single layer of low cuboidal form, the adult configuration, by the eighth day.

(d) *Supporting cells (Hensen's and Deiters')*. All of these cells can be identified at birth. They gradually increase in size and separate from each other and have a mature configuration by the eighth day.

(e) *Stria vascularis*. The stria vascularis is thin and has few blood vessels at birth (Fig. 1). It extends from the attachment of the Reissner's membrane where it is widest and tapers down to the spiral prominence. The vascularity and the thickness of the stria vascularis increase with the growth of the animal and attain normal adult dimensions by the eighth day.

TABLE 2 *Development of the N_1 and N_2 in the CBA-J mouse Mean value*

Latency in milliseconds Amplitude in microvolts N = Number of animals

Day	9	10	11	12	14
Latency N_1	1 32	1 25	1 1	1	1
Latency N_2	2 74	2 5	2 2	2 2	2 1
Amplitude N_1	33	42	58	98	222
Amplitude N_2	15	21	23	42	146
N	10	14	12	10	10

B *Action Potentials*—Clicks were used to elicit neural responses N_1 N_2 (eighth nerve action potentials as recorded at the round window), R_1 R_2 (action potentials as recorded from the eighth nerve) In the eight-day-old animal no neural responses could be elicited even though they had cochlear potentials to limited frequencies (Table 1) N_1 N_2 was found in nine-day old mice which had cochlear potential ranges from 600 to 8000 cycles per second Neural responses were absent in all of those animals having narrower cochlear potential ranges (Table 1) By the tenth day N_1 N_2 could be elicited in all the animals of the litters tested, except one This animal in litter II, had a cochlear potential range extending from 1000 to 4000 cycles per second All eleven day-old animals tested had an N_1 N_2, but with smaller amplitudes and prolonged latencies of N_1 when compared to adult responses The amplitudes and latencies attained adult values by the fourteenth day (*Table 2*)

A separate study was done in six litters to determine the development of action potentials as recorded from the eighth nerve (R_1 R_2) Animals tested on the ninth day did not have any eighth nerve action potentials On the tenth day all of the animals demonstrated an eighth nerve action potential, but the amplitudes of R_1 R_2 were less than normal The amplitudes of R_1 R_2 were normal at fourteen days of age (Table 3)

III *Behavioral Responses*

The Preyer reflex was absent in all animals tested on the eighth day (Table 1) Cochlear potential ranges were narrow in these animals By the

TABLE 3 *R_1 and R_2 development in the CBA J mouse Mean value*

Amplitude in microvolts N = Number of animals

Day	9	10	11	12	14
Amplitude R_1	—	45	83	106	162
Amplitude R_2	—	30	50	68	148
N	6	8	8	8	4

be seen by the eighth day on the scala tympani side of the basilar membrane, in the lower basal turn. The basilar membrane has normal appearance at ten days of age.

In the changes described above, it is apparent that the cochlea appears almost mature by the eighth day. It acquires a normal adult appearance at the tenth day.

II. *Physiological*

A. *Cochlear Potentials.*—Cochlear potentials were first obtained from the eight day old animal. No cochlear potentials could be elicited from the seven day old mice. The overall range present in such animals extended from 600 to 2000 cycles per second (Table 1). The intensities required to obtain 0.5 microvolt response are shown in Figure 2. This range of cochlear potentials was not present in all of the litters and the variation of range was great (Table 1). One-half of the mice tested on the eighth day did not show any cochlear potentials and those that did had only a very narrow range.

By the ninth day the cochlear potentials were present in all the litters tested, but the ranges differed (Table 1, Fig. 2). The overall range of cochlear potentials was more uniform and extended from *600 to 8000* cycles per second.

At the tenth day cochlear potentials were present in all of the animals tested. Cochlear potentials attained the adult ranges in all animals tested at eleven days of age. The sensitivity to sound was less than that present in the adult animal. By the fourteenth day the cochlear potentials had the adult ranges and sensitivity (Table 1, Fig. 2).

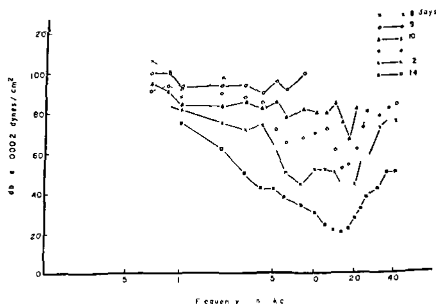


Fig. 2. Development of cochlear potential ranges in the normal hearing CBA/J mice. Plot of 0.5 microvolt cochlear potential response curve.

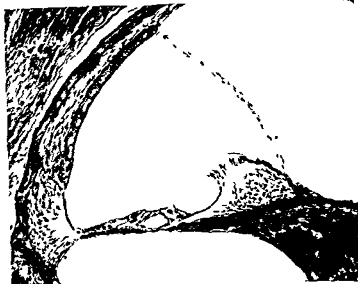


Fig 4 Cochlea of 10 day old CBA J mouse M 944 Mag ×200

Neural action potentials as recorded from the round window appeared whenever there was a cochlear potential range from 1 kc to greater than 6 kc This would indicate that to elicit an action potential, larger areas of haircell activity are needed or that more functioning units are needed to generate a recordable potential It may indicate that neural activity develops later than haircell activity



Fig 5 Cochlea of 14 day-old CBA-J mouse M 673 Mag ×200



FIG 3 Cochlea of 8 day old CBA J mouse M 594 Mag ×200

ninth day the Preyer reflex was still absent, except in one litter KK, that had a wide range of cochlear potentials and N_1 N_2

The Preyer reflex could not be elicited in two out of three of the nine-day-old animals that had N_1 and N_2 (Table 1). The Preyer reflex was *present in ten day old animals, except in only one animal of* litter II, that had a cochlear potential range from 1 to 4 kc and an absent N_1 N_2. After the eleventh day, all of the animals had developed a Preyer reflex (Table 1)

DISCUSSION

From the physiological data it is evident that the cochlear potentials appear with very narrow ranges and gradually increase to adult dimensions A similar course of events was seen also in the opossum (Larsell & McCrady, 1944) One would assume that the widening of cochlear potential ranges depends more on the presence of more active haircell units rather than anatomical changes that occur from the eighth to the tenth day The anatomical changes may aid in the sensitivity of the haircells in conveying more energy to them The loss of cochlear potentials below 1 kc, may be due to changes in the physical properties of the developing cochlea

The cochlea in the developing mouse has almost an adult configuration by the eighth day, yet there is only a limited range of cochlear potentials and no nerve action potentials The appearance of cochlear potentials one day previous to the appearance of N_1 N_2 in litter mates was also noted by Alford & Ruben (1963)

tionen erschienen wenn die Aktionspotentiale von dem achten Nerven erhalten wurden Die Entwicklung der anatomischen Veränderungen in der Maus ist vergleichbar zu denen in der Albinoratte Die Strukturen der Cochlea sind bei der Geburt vorhanden Das Cortische Organ reift allmählich bis es zwischen dem achten und zehnten Tage die Grosse des Erwachsenen annimmt Die reife Gestaltung der Cochlea bis zum zehnten Tage entspricht den Befunden des Benehmens und der Physiologie

REFERENCES

ALFORD B R, and RUBEN R J, 1963 Physiological behavioral and anatomical correlates of the development of hearing in the mouse *Ann Otol* 72 237 241

VON BÉKÉSY G, WEVER E G, RAHM E W, JR, and THOMAS RAMBO J H, 1961 A new method of perfusion for the fixation of tissues *Laryngoscope* 71 1534 1547

MCCRADY E, JR, WEVER E G, and BRAY C W, 1940 A further investigation in the development of hearing in the opossum *J Comp Physiol Psychol*, 30 17 21

LARSELL, O, MCCRADY E, JR, and ZIMMERMAN A A, 1935 Morphological and functional development of the membranous labyrinth in the opossum *J Comp Neurol* 63 95 118

LARSELL, O, MCCRADY E, JR, and LARSELL, J F, 1944 The development of the organ of Corti in relation to the inception of hearing *Arch Otolaryng* (Chic) 40 233 248

RUBEN R J, FISCH U, and HUDSON W, 1962 Properties of the eighth nerve action potential *J Acoust Soc Amer* 34 99 102

WADA T, 1923 Anatomical and Physiological Studies in the Growth of the Inner Ear of the Albino Rat Memoirs of the Wistar Institute of Anatomy and Biology no 10 Published by the Wistar Institute of Anatomy and Biology Philadelphia

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Eighth nerve action potentials were recorded from the round window in most of the animals tested on the ninth day and were present in all by the tenth day. Action potentials from the eighth nerve were recorded only in ten-day-old animals, that is to say one day after the action potentials were recorded from the round window. At present, no adequate explanation can be given for such a delay between N_1 N_2 and R_1 R_2. It would be of interest to entertain the possibility that N_1 N_2 may arise peripheral to the spiral ganglion cells. This portion of the nerve may mature physiologically before the nerve fibers in the portion central to the ganglion cells. Thus, when an electrode is placed central to the ganglion cells on the eighth nerve, there is no response even though there is an N_1 N_2 recorded from the round window membrane. This would be consistent with the behavioral observations that no Preyer response was present until the tenth day. At ten days both N_1 N_2 and R_1 R_2 were found. Ruben, Fisch & Hudson (1962) observed in the cat a discrepancy in the latency between the N_1 N_2 and R_1 R_2. This observation also suggests that the N_1 N_2 may come from some portion of the eighth nerve peripheral to the spiral ganglion cells.

A double blind study was carried out in mice seven, eight, nine and ten days old, to determine the relationship between the anatomical changes in the cochlea and the physiological and behavioral responses. The following structures were observed: The haircells and separation in between them, the tectorial membrane, the spaces of Nuel, the basilar membrane, the supporting cells and the vascularity of the stria vascularis. No anatomical difference was found between those animals with positive physiological and behavioral responses as compared to those with negative results (Figs 3, 4 and 5). The use of other methods may aid in demonstrating an anatomical and physiological correlation.

The behavioral responses correlate with the onset of the eighth nerve action potentials. Every animal with recordable potentials from the eighth nerve had a Preyer reflex. In nine-day-old mice with recordable cochlear potentials and action potentials from the round window, the Preyer reflex was absent in two out of three of the litters tested. The absence of the Preyer reflex is probably due to a physiologically immature eighth nerve because action potentials could be recorded from the eighth nerve only in animals ten days old and above.

ZUSAMMENFASSUNG

In der Maus erschienen Cochlear Potentiale zuerst in engem Band am achten Tage nach der Geburt und nahmen allmählich zu bis zum vierzehnten Tage wenn die Reaktionen die Werte der Erwachsenen erreichten. Nerv Aktionspotentiale wurden am runden Fenster aufgenommen und erschienen am neunten Tage wenn sich das Band der Cochlear Potentiale von 0.6 zu 8 Kc (Hertz) erstreckte. R_1 R_2, wenn vom achten Nerven aufgenommen, erschienen einen Tag nachdem N_1 N_2 von der runden Fenster Membran aufgenommen wurde. Die Preyer Reak

five of the children had normal hearing and eight perceptive hearing loss. During an observation time of 1 1/2 to 9 years hearing impairments were observed in the children with primarily normal hearing, and the hearing impairments in the other children became more severe. The cause of these defects could not be established but the author mentions the possibility of hereditary etiology. During a period of 7 years Williams & Roblee (1962) observed a family consisting of a mother and her three children with perceptive hearing loss. All of them had audiograms with basin curve and no progressivity could be registered during that time.

An exogenous factor that may be of a certain significance as a contributing cause of progressivity of already existing hearing impairment is the constant use of a hearing aid. The modern hearing aids have a high acoustic output with values of up to 130–135 dB SPL, some aids still higher values. Many of the severely impaired children use their aids all day and are hereby more or less permanently exposed to sound pressures that are known to cause hearing impairment in normal ears. The literature on the possibility of impairing effects of hearing aids contains very few contributions, however. Moller & Rojskjaer (1960) observed 390 cases of perceptive hearing impairment for more than 5 years during which period hearing aids had been used regularly. In nine of these cases tone audiograms showed a distinct progression of the hearing loss on the hearing aid ear. The maximum output of the hearing aids was 120 dB in all these cases. The material included age groups from 10 to 78 years.

Kinney (1961) studied 178 children who had been using hearing aids for more than one year. Out of 126 children who had been using hearing aids with an ordinary maximal output (no values given) 13 children showed a progression of the hearing impairment on the hearing aid side according to the tone audiogram. In four of these children progression was found on the other ear too. In the remaining 52 cases hearing aids with a maximum output of up to 146 dB SPL had been used. Out of 39 children who had been using such hearing aids on one ear only 19 showed progression, and 9 out of the 13 children who had been using two hearing aids (stereo-application) demonstrate a distinct progression on both ears. The noxious effect of hearing aids in relation to etiology is not reported but according to the author's opinion, hearing defects due to hereditary factors are the most resistant against hearing aid trauma.

The aim of the present investigation has been to establish if hearing loss in children is progressive and if so if there is any difference in this respect between the exogenous and the endogenous defects. As the majority of the children in this study have been using hearing aids regularly it should be possible to detect if hearing aid trauma can cause a further deterioration of the impairment.

MATERIAL

During the last 15 years more than 1000 deaf and severely hard of hearing children have been examined and continuously followed up at the

PROGNOSIS OF PERCEPTIVE HEARING LOSS IN CHILDREN WITH RESPECT TO GENESIS AND USE OF HEARING AID

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Eighty-four children with bilateral perceptive hearing loss have been followed up during a period of up to 15 years from the first reliable hearing test. The material has been grouped according to the probable causes of hearing defect. The cases with exogenous (acquired) hearing loss include three different groups: (A) Maternal rubella, (B) Perinatal accident, (C) Meningitis with or without dihydrostreptomycin treatment. The other main group includes cases in which the hearing loss is assumed to be of endogenous (hereditary) genesis. During the time of observation the majority of children had been using hearing aids regularly.

None of the children with hearing impairment due to exogenous factors caused by maternal rubella or acquired perinatally showed any signs of progressivity despite the constant use of a hearing aid.

All cases of hearing impairments caused by meningitis with or without dihydrostreptomycin treatment, however, showed progressivity of the hearing impairment. Whether the use of a hearing aid contributes to this progressivity or whether it is spontaneous cannot be definitely established. Spontaneous progressivity seems most likely however.

More than half of the reported hereditary cases with hearing impairments showed spontaneous progressivity. This progressivity has been characterized by a certain irregularity. During long periods of time the hearing impairment seems to be stationary, but suddenly progresses rapidly. The progress can either be bilaterally symmetric or asymmetric. Progressivity is probably not due to the use of a hearing aid, but spontaneous and due to hereditary factors.

Progressive perceptive hearing loss in children was already observed by Politzer (1901), Manasse (1906), Alexander (1927) and others, but no thorough etiologic studies had been conducted in these cases. Albrecht (1923), Goodhill (1950), Johnsen (1952), Ford (1952), Dolowitz & Stephens (1952), Cawthorne & Hinchcliffe (1957) and others reported progressive perceptive hearing loss in cases with hereditary genesis. In these cases the authors have been using anamnestic data to prove progressivity. Repeated hearing tests to demonstrate progressivity have, however, not been made.

Brockman (1959) examined 13 children, 8 boys and 5 girls, who were audiometrically tested for the first time at the age of 4 to 8 years. Primarily,

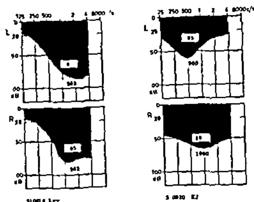


Fig. 1. Follow up examinations in children with exogenous (acquired) hearing impairments. Typical audiograms in cases with hearing loss and cerebral palsy caused by perinatal anoxemia (LST) and in cases with hearing loss caused by maternal rubella (EJ), none of them showing progress during time of observation. Black area: Hearing loss at first examination and follow up. L = left, R = right ear.

but only where the case history has been considered to be reliable. All these children are included in the material of an earlier study (Barr & Lundström 1958). In most cases the hearing loss in this group of children is bilateral of flat loss or basin shaped type and asymmetric in respect to the degree of hearing loss between the right and left ear (Fig. 1, EJ).

None of the children showed an established progression of the hearing impairment during observation time. In two of the children a threshold elevation of 15 dB was observed at 125 c/s, but on the other hand two children showed a similar threshold lowering at that frequency.

All children in this group had regularly been using hearing aids, as a rule always on one and the same ear.

B. *Perinatal accidents*

This group includes 15 children with an observation time of 5 to 10 years. Concomitant with the hearing impairment ten of the children suffered of cerebral paresis of varying severity. The material constitutes a comparatively heterogeneous group in which, after thorough investigation, the children have been considered to have been exposed to severe anoxemia at the time of birth (anoxemia combined with prematurity < 1500 g, severe icterus, birth injuries etc.). Tone audiograms of children of this group show varying degrees of high tone hearing impairment bilaterally symmetric (Fig. 1, LST). Only one of the children shows asymmetry in this respect and in this case one ear is totally deaf.

In none of these children the hearing impairment showed any progressivity according to the above criteria. In two cases a certain lowering of the hearing threshold with 10–15 dB was observed at 125 c/s and 250 c/s. All

Department of Paedo-Audiology, Karolinska Hospital, Stockholm Out of this material one main group with a probable exogenous cause of the hearing defect have been selected and classed into three different sub groups each including a sufficient number of children to make the material representative The sub-groups consist of children with hearing loss caused by (*a*) maternal rubella, (*b*) perinatal accidents and (*c*) meningitis with or without dihydrostreptomycin treatment The comparison group of children with endogenous hearing impairment consists of cases reported in an earlier study by one of the authors (Wedenberg, 1965)

Hearing Tests

Conventional octave audiometry in the frequency range of 125–4000 c/s has been applied in the majority of hearing tests At their first examination, however, a great number of children have been too young to be tested with this method, and in these cases a play audiometric procedure has been applied (Barr, 1955) At the first and all following examinations, several tone audiograms were taken, and the threshold values were not regarded reliable until several tone audiograms agreed Deviations of more than 5 dB were not permitted except for the frequencies 125 and 250 c/s for which a deviation of 10 dB was accepted Some of the children were below the age at which play audiometric tests are applicable In such cases the hearing examination has been carried out by applying the auro-palpebral reflex test and the wakening test (Wedenberg, 1963) This method is assumed to be very reliable in establishing a hearing impairment even in newborn children To a certain extent even the type and degree of a hearing loss can be determined

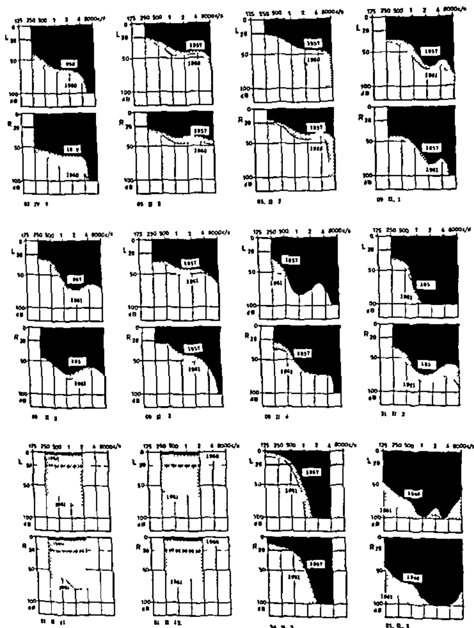
Some of the older children were tested by Bekesy audiometry at their first examination In these cases the follow-up tests also were performed with the same method The calibration of all audiometric equipment has been checked regularly, and the tests have been conducted under uniform conditions

A deviation of at least 10 dB at two test frequencies or 15 dB at one test frequency, has been defined as a change of hearing threshold For the frequency 125 c/s, however, the deviation had to exceed 15 dB to be regarded as significant

Presentation of the Various Groups and Result of Hearing Test Exogenous (Acquired) Hearing Impairment

A *Maternal rubella*

This group includes 23 children with an observation time of 5 to 11 years In practically all cases the diagnosis maternal rubella has been confirmed by physicians A few cases without doctors diagnosis have been included



The reported cases have hearing remnants, however, and all cases are progressive

Hearing aids have been used regularly In the only case with hearing remnants in both ears, the ear in which the child had been using the hearing aid showed the lower degree of progressivity (Fig 2, LN, right ear)

Fig. 2. Follow-up examinations in children with exogenous (acquired) hearing impairments. Audiograms from six children with hearing loss caused by meningitis. Three of the children (LN, GA and BKL) were treated with dihydrostreptomycin. Black area: Hearing loss at first examination. Dotted area: Progress of hearing loss from first examination. L = left. R = right ear.

children had been using hearing aids regularly, as a rule on one and the same ear.

C. *Meningitis—dihydrostreptomycin*

This group includes six children with an observation time of 7 to 10 years (Fig. 2). All children have had meningitis and three of them had been treated with dihydrostreptomycin.

All children suffer of a severe hearing loss and, with the exception of one, total deafness on the opposite ear. Whether the hearing impairments have been caused by meningitis or the ototoxic effects of dihydrostreptomycin could not be established.

The small number of children in this group is due to the fact that in children meningitis affecting the hearing usually leads to total deafness.

defects of probable endogenous origin in the family could be pointed out. In 35 families at least two children in every family had hearing impairment. The extremely carefully obtained case histories and medical examinations found nothing to indicate an exogenous cause of the hearing impairments. In our present state of knowledge it seems justified to conclude that the majority of hearing defects in this group of children are due to hereditary factors. The hearing of all parents was tested by Békésy audiometry and a great number of clinical and also previously unknown subclinical hearing defects could be demonstrated.

It is known that in the majority of acquired hearing impairments the highest frequencies are primarily affected. To avoid a possible involvement of acquired hearing impairments the classification of hearing defects as being of a probable hereditary origin has been restricted to purely perceptive impairments below 3000 c/s. A great part of the hearing defects found in these parents were subclinical. They showed a characteristic dip or basin in the frequency range below 3000 c/s readily distinguished with the continuous recording technique of the Békésy audiometer. To be considered significant these subclinical hearing defects had to cover at least over one octave with a minimum loss of at least 20 dB and at least 6 dB at the edges of this frequency range. In an average material of persons with subjectively normal hearing and without hereditary case histories such deviations can be found in less than 5%. This type of subclinical hearing abnormalities is quite common in the hereditary parent group. It has therefore been considered justifiable to classify such a defect in a parent as a hearing loss, although the threshold elevation may be too small to cover the general conception of this expression.

In the majority of cases with hearing impairments due to hereditary factors the hearing loss was so severe that no comparative examinations with respect to progressivity was possible. Forty cases, however, that have been followed 3 to 15 years after the first examination had hearing remnants of such a degree that a follow up was possible. Twenty two out of these 40 show distinct progressivity (Fig. 3).

Of the 22 cases with progressive hearing loss 7 had been using hearing aids. However, only 2 of these cases had used the aids *regularly enough to permit conclusions. One of them showed greater progressivity in the aidless* ear and the other demonstrated approximately the same *degree* of progression bilaterally in spite of the fact that they both used their aids in one and the same ear during the observation time. *In five cases the hearing* aid had either been moved from one ear to the other or irregularly used. The following case reports are given as examples.

Cases 21 II 2, 21 II 11 and 21 II 12 (Fig. 3).—The mother suffers of a severe hearing loss that developed at the *age of 20* and progressed. She has born 12 children, 10 boys and 2 girls (one girl died). According to the father (normal hearing) the children began to pronounce single words at the age of one. Gradually they formed two word sentences as children with normal hearing do. At the

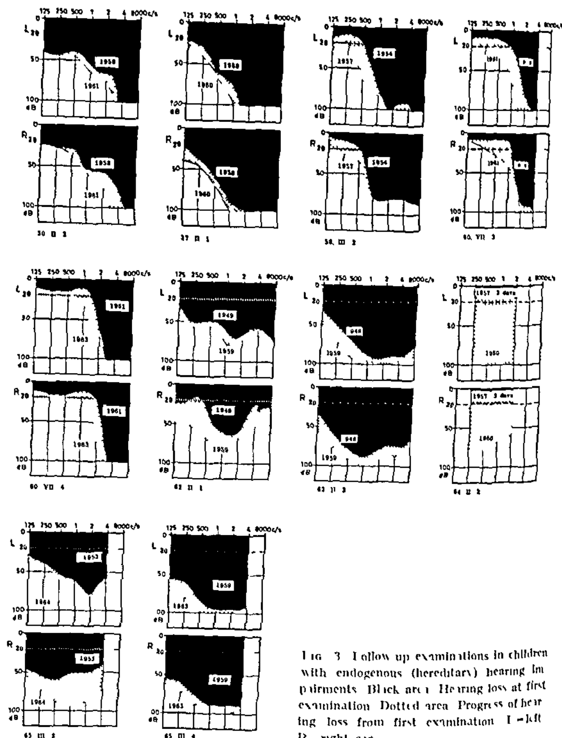


FIG. 3. Follow up examinations in children with endogenous (hereditary) hearing impairments. Black area: Hearing loss at first examination. Dotted area: Progress of hearing loss from first examination. L = left, R = right ear.

Endogenous (Hereditary) Hearing Impairments

The material forming this second main group is selected from 111 hard of hearing children in 56 families. In 46 of the families the anamneses showed one or several cases of hearing impairment — the probands excepted — without known exogenous cause. In ten of the families the parents were related, cousins or second cousins and in four of these marriages hearing

defects of probable endogenous origin in the family could be pointed out. In 35 families at least two children in every family had hearing impairment. The extremely carefully obtained case histories and medical examinations found nothing to indicate an exogenous cause of the hearing impairments. In our present state of knowledge it seems justified to conclude that the majority of hearing defects in this group of children are due to hereditary factors. The hearing of all parents was tested by Bekesy audiometry and a great number of clinical and also previously unknown subclinical hearing defects could be demonstrated.

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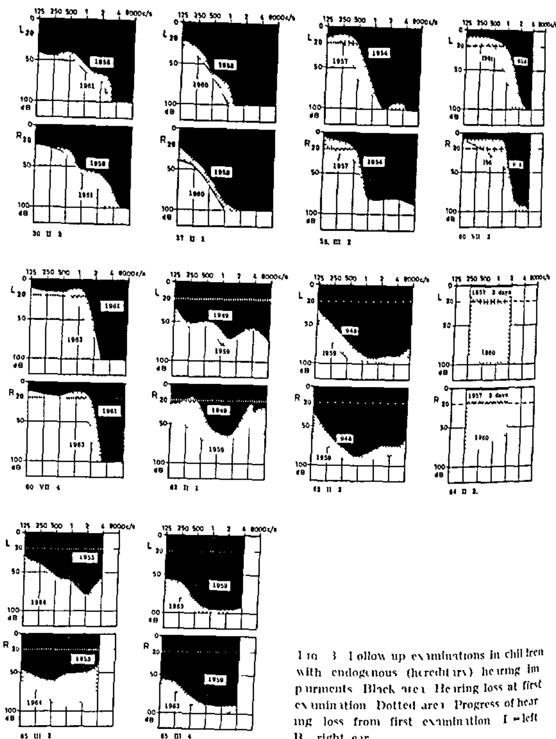


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generations. The first cases of hearing impairments are recorded around 1800. In a marriage (in which no hearing loss had occurred) 7 children were born of which four had hearing impairments. They attended the school for the deaf in Stockholm. The entrance documents and school results show that the children had not been totally deaf when entering the school but that they gradually lost their hearing completely. The entrance document says, 'Hears and speaks a little, but not clearly.' One of the deaf sons in this family married a woman who had shown signs of a beginning hearing loss at the age of 7. Four boys were born of whom two lost their hearing gradually. One of them married a woman who at the age of 7 had lost her hearing following meningitis. In their marriage they had two boys. One of them gradually lost his hearing and was totally deaf at the age of 17. He married twice. First with a normal hearing woman, who gave birth to a son that still hears normally at adult age. His second wife had gradually lost her hearing (as did her brother) and was nearly totally deaf at the age of 8 or 9. In this second marriage two sons were born (60 VII 3 and 60 VII 4), who probably have had normal hearing as infants. Their speech is well developed and modulated but comparative measurements of hearing show an increasing impairment.

DISCUSSION

Hearing impairments in children of definitely exogenous nature caused by maternal rubella or perinatal accidents do not show any progressivity despite the permanent use of a hearing aid during an observation time of up to 11 years.

Hearing impairments caused by meningitis with or without dihydrostreptomycin treatment however all show progressivity. It could not be established whether the use of a hearing aid contributes to this progressivity or whether it is spontaneous. However, the suspicion of a spontaneous deterioration of hearing is supported by the fact that in the only case with hearing remnants in both ears the hearing aid ear shows the lowest progressivity.

By microscopic examination of inner ears in which inflammatory processes have taken place Hallpike (1964) has been able to demonstrate histological changes which may continue several years after the healing of the acute affection. This suggests a very long postinfection condition during which changes in the hearing acuity may be expected until the hearing loss reaches its definite character. It is also known from examinations of adults that hearing loss following dihydrostreptomycin treatment can continue to increase long time after the treatment has been discontinued (Shambaugh *et al* 1959). It therefore seems more likely that progressivity of hearing loss is due to the illness itself or its treatment rather than the use of a hearing aid.

The progressivity of the hearing loss found in the hereditary cases has been characterized by a certain irregularity. It seems that a hearing defect can be stationary for a long period of time and then rapidly progress. The [illegible] symmetric or asymmetric. Three cases

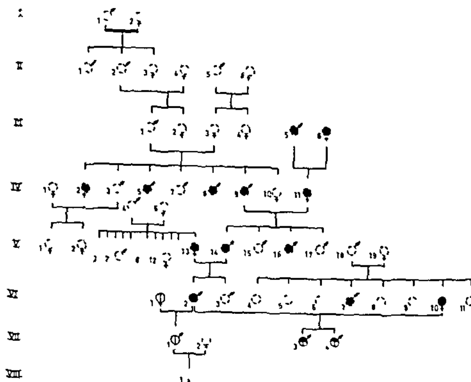


FIG 4 Pedigree of eight generations in which the affected individuals (half filled or full circles) became gradually hard of hearing or deaf (Cases 60 VII 3 and 60 VII 4)

age of two the father noticed that their speech capacity was not on the same level as that of other children, and their hearing was obviously impaired Hearing tests at preschool and school age showed severe hearing defects of the same type as their mother's, but was less pronounced the younger the children were A certain slow progress then took place, and at the age of twenty the audiograms of the oldest children were very similar to their mother's audiogram The father's statement that the children's hearing had been quite normal during their first year of life was naturally met with great scepsis One of the authors examined the eleventh child (21 II 11) a boy, at the age of one, and found his hearing to be quite normal Two years later he had a severe hearing impairment The twelfth child (21 II 12) was examined at the age of 1 month and reacted normally to sound stimuli At the age of three years the child had a hearing loss of the same type as the other children It therefore does not seem unlikely that the other children had normal hearing during their first year of life as their father had stated

Case 61 II 2 (Fig 3) —Both parents are deaf The child's hearing was tested at the age of three days The test was repeated on the 6th and 9th day with the same result normal hearing bilaterally A hearing test at the age of three years showed a severe bilateral hearing impairment

A hearing aid had not been used until after the age of three years

Cases 60 VII 3 and 60 VII 4 (Figs 3 and 4) —By means of church documents court records, school entrance and other documents it has been possible to follow the family history of the father to the beginning of the 16th century including 15 generations, and of the mother to the beginning of the 19th century including 6

gruppe besteht aus hereditäre Hörstörungen. Die meisten der Kinder haben während der Observationszeit regelmässig Hörapparate angewendet.

Trotz dauernder Anwendung von Hörapparaten weisen die mit Sicherheit exogen bedingten Hörstörungen, die bei den Kindern durch Röteln verursacht oder perinatal erworben worden sind, keine Progressivitätszeichen auf. Hörstörungen, die durch Meningitis oder Dihydrostreptomycinbehandlung verursacht worden sind, weisen dagegen alle eine Progressivität auf. Ob die Anwendung von Hörapparaten zu dieser Progressivität beiträgt, oder ob sie spontan ist, kann nicht mit Sicherheit entschieden werden. Vieles spricht jedoch für spontane Progressivität.

Über die Hälfte der vorliegenden hereditären Hörstörungen weisen spontane Progressivität auf. Charakteristisch für diese Progressivität ist eine gewisse Unberechenbarkeit. Während einer langen Zeitdauer von mehreren Jahren scheint die Hörstörung stationär zu sein, schreitet jedoch dann sehr rasch fort. Der Progress ist manchmal bilateral symmetrisch, manchmal asymmetrisch. Die Progressivität dürfte der Anwendung von Hörapparaten nicht zugeschrieben werden können, sondern gänzlich auf einer spontanen, genetisch bedingten Entwicklung beruhen.

REFERENCES

ALBRECHT, W., 1923. Über die Vererbung der konstitutionell sporadischen Taubstummheit, der hereditären Labyrinthschwerhörigkeit und Otosclerose. *Arch Ohr Nas Kehlkopfheilk* 110 15

ALEXANDER, G., 1927. *Die Ohrenkrankheiten im Kindesalter*. Verlag von F. C. W. Vogel

BARR, B., 19[illegible]. Pure tone audiometry for pre school children. *Acta Otolaryng* (Stockh.), Suppl. *110*

BARR, B., and LUNDSTROM, R., 1958. Deafness following maternal rubella. *Acta Otolaryng* (Stockh.) [illegible] 413

BROCKMAN, S. J., 1959. An exploratory investigation of delayed progressive neural hypacusis in children. *Arch Otolaryng* (Chic.) *70* 340

CAWTHORNE, T. [illegible] and HINCHCLIFFE, R., 1957. Familial perceptive deafnesses. *Pract Oto-rhino-laryng* (Basel) *19* 69

DOLOWITZ, D. A., and STEPHENS, F. E., 1952. Hereditary progressive nerve deafness. *Trans Amer Acad Ophthal Otolaryng* *56* 457

FORD, F. R., 1952. Diseases of the nervous system in infancy, childhood and adolescence. Thomas, Springfield

GOODHILL, V., 1950. The nerve deaf child: significance of Rh, maternal rubella and other etiologic factors. *Ann Otol* 59 1123

GRÜNEBERG, H., HALLPIKE, C. S., and LEDOUX, A., 1940. Observations on the structure, development and electrical reactions of the internal ear of the shaker 1 mouse (mus musculus). *Proc Roy Soc Med* *129* 154

HALLPIKE, C. S., 1964. Personal communication

JOHNSEN, S., 1952. The heredity of perceptive deafness. *Acta Otolaryng* (Stockh.) 42 [illegible]

KINNEY, C. E., 1961. The further destruction of partially deafened children's hearing by the use of powerful hearing aids. *Ann Otol* *70* 828

MANASSE, P., 1906. *Über chronische progressive labyrinthäre Taubheit*. Wiesbaden

M[illegible], T. T., and RÖJSKJAER, C., 1960. Injury to hearing through hearing aid treatment. Fifth Congr. of Intern. Soc. of Audiol., Bonn, Germany

POLITZER, A., 1901. *Lehrbuch der Ohrenheilkunde*. Stuttgart

SHAMBAUGH, G. E. JR., DERLACKI, E. L., HARRISON, W. H., HOUSE, H., HOUSE, W., HILDYARD, V.,

where the hearing impairment was diagnosed in the first year of life demonstrated an extremely rapid progress.

Either in the hereditary material the traumatic effect by hearing aids reported by Kinney (1961) could be verified. The majority of the reported cases in our study have been progressive although hearing aids had not been used. In the few cases where hearing aids had been used regularly progressivity was greater in the aidless ear in one case, and in one case the progression was as severe in the ear using a hearing aid as in the ear that had been without. In eight cases in which a hearing aid has been used no progressivity was observed despite continuous use. It consequently appears reasonable to assume that the traumatic effects of a hearing aid, if any, are of minor importance compared to spontaneous impairment. This observation agrees well with those made by Moller & Rojskjaer (1960) in their investigation.

In his study Kinney (1961) does not mention the genesis of the hearing defects of his material, but probably the number of cases of hearing defects due to hereditary factors is comparatively great. Consequently it seems most probable that the progressivity found by Kinney has its cause in a spontaneous impairment of the hereditary defects or possibly in defects of the meningitis dihydrostreptomycin type.

It would be unrealistic, however, to deny the possibility of injuring effects due to permanent use of an extremely high powered hearing aid. To be permitted for distribution in Sweden all high power hearing aids must be equipped with an output limiter. Most of the hearing aid types used by the children in this study have had an output limit below 130 dB SPL and no aid type above 138 dB. Kinney reports cases in which hearing aids with a maximum output of up to 146 dB have been used, and at such intensities the risks for a trauma are quite obvious.

The endogenous hearing defects that appear in earlier infancy of human beings have their correspondence among animals. It has been known for a long time that certain races of animals (rats, guinea pigs) can hear when they are born but lose their hearing capacity during their first months of life. Histologic studies have shown that in these animals the cochlea is normally developed at birth but degenerates gradually (Gruneberg *et al* 1940).

ZUSAMMENFASSUNG

81 Kinder mit doppelseitigen neurogenen Hörstörungen wurden während einer Zeitdauer von 3 bis zu 15 Jahren nach den ersten zuverlässigen Gehörtesten nachuntersucht. Das Material ist in Bezug auf die wahrscheinlichen Ursachen der Hörstörungen eingeteilt worden: exogene und endogene Hörstörungen. Die exogenen Hörstörungen besteht aus drei Gruppen, die eine derartig grosse Anzahl von Kindern repräsentieren, dass sie eine gute Beurteilungsbasis bilden dürften: (A) Röteln-Infektion während der Schwangerschaft, (B) Perinatal erworben, (C) Meningitis mit oder ohne Dihydrostreptomycinbehandlung. Die andere Hauptgruppe

UPPER AIRWAY RESISTANCE DURING MOUTH BREATHING IN PATIENTS WITH UNILATERAL AND BILATERAL PARALYSIS OF THE RECURRENT LARYNGEAL NERVE

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The upper airway—subglottic to mouth—resistance was measured as the relationship between the pressure drop across and flow through this part of the respiratory tract in 10 male and 5 female cases of unilateral and 1 male and 9 female cases of bilateral paralysis of the recurrent nerve. The pressure flow relationship was curvilinear during both inspiration and expiration and both resting and hyperventilation. All curves could be represented in terms of second degree polynomials. Means of upper airway resistance at a flow rate of 0.5 l/sec were 1.0 and 0.9 cm H_2O/l/sec at rest and during hyperventilation respectively, in male cases of unilateral paralysis of the recurrent nerve. Corresponding values for female cases were 1.1 and 2.0 cm H_2O/l/sec. In cases of bilateral paralysis the mean upper airway resistance at a flow of 0.5 l/sec at rest was 21.5 cm H_2O/l/sec. The mechanical work performed in moving air through the upper airway was determined as the cumulative product of ventilated volume and pressure drop across this segment of the tract. The mean value during resting ventilation was 0.009 kpm[1]/l of V_E for male cases and 0.024 for female cases of unilateral paralysis of the recurrent nerve. For bilateral cases it was 0.074 kpm/l of V_E. Eight unilateral and 3 bilateral cases of paralysis of the recurrent nerve were examined by static and dynamic spirometry. All of them showed low or subnormal values of MVV_E.

INTRODUCTION

In the normal subject 1[illegible]50 % of the total airway resistance in mouth breathing is accounted for by the upper airway—that is, the oral cavity, the pharynx and the larynx (Ferris, Opie & Mead 1960, Hyatt & Wilcox 1961, Schiratzki 1964). The resistance to a gas flowing through a tube increases when the cross-sectional area decreases, other conditions unchanged. A stenosing process in the airway would therefore increase the airway resistance. In cases of unilateral paralysis of the recurrent nerve

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SCHLINECHT and SHEA J J 1959 Dihydrostreptomycin deafness *J Amer Med Ass* *170* 1657
WEDENBERG E 1954 Auditory training of severely hard of hearing preschool children *Acta Otolaryng* (Stockh) Suppl *121*
— 1963 Objective auditory tests on non cooperative children *Acta Otolaryng* (Stockh) Suppl *175*
— 1965 *Acta Otolaryng* (Stockh) To be published
WILLIAMS F and ROBIFF I A 1962 Hereditary nerve deafness A follow up of 4 cases in one family *Arch Otolaryng* (Chic) 75 69

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TABLE 1 *Clinical findings relating to 10 male and 5 female cases of unilateral paralysis of the recurrent nerve*

	Subject	Age	Dyspnoea	Cause of cord paralysis	Chest X ray examination	Comments
Men	RI	46	No	Unknown	Normal	
	RK	27	No	Thyroidectomy	Moderate preoperative tracheal compression otherwise normal	
	GL	73	No	Unknown	Shrinking process in upper part of right lung hilar calcification	
	EW	42	No	Unknown	Normal	
	TA	28	No	Unknown	Normal	
	EK	26	No	Cervical operation	Slight parenchymal infiltration under pleura at right apex	
	HJ	49	No	Pulmonary carcinoma	Pulmonary tumour	
	MH	33	No	Pulmonary carcinoma	Pulmonary tumour	
	GAS	65	No	Cervical operation	Normal	
	EuA	54	No	Cranial tumour	Normal	Palatal and pharyngeal paralysis
Women	SL	58	No	Thyroidectomy	Normal	
	EA	68	No	Thyroidectomy	—	No physical signs of lung disease
	AA	70	Yes	Unknown	Normal	Periods of inspiratory stridor
	LO	44	No	Intracranial tumour	Moderate thickening basally right	Palatal and pharyngeal paralysis
	KH	6[illegible]	No	Unknown	Calcified hilar lymphomas	

METHOD

Terminology and Definitions

The symbols used are those suggested by Pappenheimer *et al* (1950)

Spirometric study

The total lung capacity and its subdivisions were determined by the helium dilution method (Holmgren 1954) with a closed spirometer system The values found were expressed as a percentage of those predicted from normal values published by Grimby & Soderholm (1963)

The vital capacity and forced expiratory volume in one second were determined and the one second value was also given as a percentage of the

with the vocal cord in the midline position the area open for the airstream would probably be less than in normal subjects. In bilateral paralysis with both cords in the midline position the aperture is but a fraction of the normal area. In cases of paralysis of the recurrent nerve an increase in the airway resistance would therefore be expected. The magnitude of this increase would depend on whether or not the state is unilateral or bilateral. An increase in the upper airway resistance would in turn be expected to result in respiratory disturbances.

It is generally accepted that unilateral cord paralysis rarely gives rise to breathing difficulties at rest, although vigorous exercise can cause ventilatory distress (Berendes 1936, Jackson & Jackson 1959). In bilateral paralysis, on the other hand, there is invariably difficulty in breathing, ranging from mild dyspnoea to the most severe symptoms and even suffocation (Carlens 1954, Berendes 1956).

The object of the present investigation has been to examine the upper airway resistance and the upper respiratory mechanical work in cases of unilateral and bilateral paralysis of the recurrent nerve. This was done by means of conventional spirometric examinations, study of the pressure-flow and the pressure–volume relationships in the upper airway of these patients and comparison of the results with those in normal subjects.

MATERIAL

The material consisted of two groups of patients—one with unilateral and the other with bilateral paralysis of the recurrent nerve. All were examined by indirect laryngoscopy. The presence of an immobile vocal cord in or near the midline was taken as proof of paralysis of the recurrent nerve on that side.

The group with unilateral paralysis consisted of 10 men and 5 women (mean ages 45.3 and 61.0 years, respectively). The bilateral paralysis group comprised one man and 9 women. The mean age of this group was 55.5 years. One woman in this group had undergone a cordopexy operation but without any signs of relief, the cord remaining in the midline position.

Clinical data on the patients are given in Tables 1 and 2.

No patient was included in the spirometric examination for whom there was evidence of respiratory disturbances that could not be attributed to the laryngeal stenosis. Thus, 3 of the cases of unilateral paralysis were excluded on grounds of pathologic chest X-ray findings. Four others did not take part in this investigation for non-medical reasons. One patient of the bilateral paralysis group was excluded owing to previous poliomyelitis. Four patients were tracheotomized and were unable to breathe through the mouth. Two patients of the bilateral group were excluded because of pathologic chest X-ray findings.

TABLE 1 *Clinical findings relating to 10 male and 5 female cases of unilateral paralysis of the recurrent nerve*

	Subject	Age	Dyspnoea	Cause of cord paralysis	Chest X-ray examination	Comments
Men	RI	46		Unknown	Normal	
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	GL	73		Unknown	Shrinking process in upper part of right lung hilar calcification	
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	TA	28		Unknown	Normal	
	FK	26	No	Cervical operation	Slight parenchymal infiltration under pleura at right apex	
	HJ	49		Pulmonary carcinoma	Pulmonary tumour	
	AH	33		Pulmonary carcinoma	Pulmonary tumour	
	GVS	65		Cervical operation	Normal	
	TuA	54		Cranial tumour	Normal	Palatal and pharyngeal paralysis
Women	SL	58		Thyroidectomy	Normal	
	FA	68		Thyroidectomy	—	No physical signs of lung disease
	AA	70	Yes	Unknown	Normal	Periods of inspiratory stridor
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The vital capacity and forced expiratory volume in one second were determined and the one second value was also given as a percentage of the

Table 2. *Clinical findings relating to one male and 9 female cases of bilateral paralysis of the recurrent nerve*

	Subject	Age	Dyspnoea	Tracheotomy	Cause of cord paralysis	Chest X-ray examination	Comments
Women	EdW	71	Severe	No	Thyroidectomy	Normal	
	LE	57	—	Yes	Thyroidectomy	Normal	
	IsW	52	Varying	No	Poliomyelitis	Normal	Unsuccessful cordopexy, tracheotomized soon afterwards
	GS	65	—	Yes	Thyroidectomy	Normal	
	IS	40	Moderate	No	Thyroidectomy	Normal	
	IW	45	Moderate	No	Thyroidectomy	Normal	Tracheotomized soon afterwards
Man	ND	66	Severe	No	Cerebral lesion	Pronounced emphysema	Tracheotomized soon afterwards
Women	KL	48	Severe	No	Thyroidectomy	Changes as in healed tuberculosis right lung	
	LJ	74	—	Yes	Thyroidectomy	Normal	
	AA	70	—	Yes	Thyroidectomy	Normal	

highest value for the vital capacity (Berglund *et al.*, 1963). These values were expressed as a percentage of those from normal values published by Berglund *et al.* (1963).

The maximum voluntary ventilation at a free rate was measured by means of the Bernstein spirometer (Bernstein, D'Silva & Mendel, 1952) and expressed as a percentage of the normal values reported by Grimby & Söderholm (1963). All values outside twice the standard deviation of the normal series reported above were regarded as abnormal.

Upper airway resistance

The method, apparatus and procedure has been described in detail elsewhere (Schiratzki, 1964) and it will suffice to outline them here in brief.

To measure the upper airway resistance it is necessary to record simultaneously the volume-flow through and pressure gradient across this part of the respiratory tract. The cricothyroid membrane was punctured with a special needle and the difference between the lateral pressure in the subglottic space and that at the oral aperture was measured by means of an electrical differential manometer. The volume flow was measured with a Fleisch pneumotachograph connected to an electrical pressure transducer. Pressure-flow curves were obtained by recording both variables on an oscilloscope; these images were photographed and enlarged to common scales, one for the unilateral and another for the bilateral paralysis groups. Curves were obtained for both inspiration and expiration. The unilateral

paralysis cases were examined during resting ventilation and moderate hyperventilation. When instructed to hyperventilate, most of the patients with bilateral paralysis did not increase their respiratory flow rate, and the hyperventilation examination was therefore omitted for this group. The pressure–flow curves were integrated by planimetry for flow rates from zero to 0.25 and 0.50 l/sec in all experiments. Second degree polynomials of the type $P = k_1\dot{V} + k_2\dot{V}^2$ were fitted to the pressure–flow curves, the coefficients being determined by means of these integrals (Schiratzki 1964). The pressure difference across the upper airway was calculated from the equations for the flow rates 0.25, 0.50 and, during hyperventilation, also 1.00 l/sec, irrespective of whether this flow rate was achieved. In the cases of bilateral cord paralysis the pressure difference was not calculated for 1.00 l/sec because the extrapolation was regarded as being too large.

For measurement of the subglottic pressure only the tracheotomized patients required a special procedure. The tracheal cannula was removed and a Magill endotracheal tube, cut above and below the cuff, was introduced into the tracheostoma. The cuff was insufflated to press against the walls of the stoma. Care was taken that the tube should not protrude into the lumen of the trachea. During the short time covered by the experiment the outer end of the tube was closed with a rubber stopper so that the patient was obliged to breathe through the stenosed larynx. The rubber stopper had previously been punctured with a needle similar to that used to puncture the cricothyroid membrane of the patients not tracheotomized.

Upper respiratory mechanical work

To determine the upper respiratory mechanical work, ventilatory volumes were measured by electrical integration of the flow signal. Volume was then plotted against pressure difference on an oscilloscope. Studies were performed only in resting ventilation.

Statistical analysis

The two groups of the material were subdivided as follows:

Unilateral paralysis of the recurrent nerve	men	resting ventilation	inspiration expiration	Fig. 1 A
		hyperventilation	inspiration expiration	Fig. 1 B
	women	resting ventilation	inspiration expiration	Fig. 1 C
		hyperventilation	inspiration expiration	Fig. 1 D
Bilateral paralysis of the recurrent nerve		resting ventilation	inspiration expiration	Fig. 7

On the assumption that the breathing pattern can be approximated to a sine wave with the same mean flow for all patients, the above mentioned integrals can be used for comparison of airway resistance (Schiratzki 1964).

Thus the resistance during different breathing manoeuvres was compared by determining the mean difference between the respective integrals and examining its significance by the *t* test. Different groups were compared on the basis of their mean integrals and the significance of the differences between them.

RESULTS

Unilateral Paralysis of the Recurrent Nerve

Spirometry

Eight of 1[illegible] patients were examined by spirometry. One patient had a fairly high FRC (134 %)[1] and RV (147 %) but the FRC/TLC and RV/TLC quotients were within normal limits. Small TLC (75 %) and VC (69 %) were found in another patient. The FRC/TLC quotient was increased in 2 patients (123 % and 132 %) and in the latter there was also a high value of FRC (143 %). One patient presented a low VC (71 %).

The results of the dynamic spirometry were normal except that the FEV % was abnormally low for one patient, being 85 % of the predicted value. In 4 of the patients the values for MVV_F were outside the normal limit (53, 53, 44 and 35 %). For the other 4 patients the values were low. The means for the men and women were 62 and 50 % respectively (Table 3).

TABLE 3. *Total lung capacity (TLC), vital capacity (VC), functional residual capacity (FRC), residual volume (RV), functional residual (FRC/TLC) and residual quotients (RV/TLC), forced expiratory volume in one second, expressed in absolute values ($FEV_{1.0}$) and in relation to forced vital capacity (FEV %) and maximum voluntary ventilation at a free rate (MVV_F), 4 men and 4 women with unilateral paralysis of the recurrent nerve*

All values expressed as a percentage of predicted values. Values outside twice the standard deviation are in bold face

	Subject	TLC	VC	FRC	RV	FRC/TLC	RV/TLC	$FEV_{1.0}$	FEV %	MVV_F
Men	RP	[illegible]	116	**134**	**147**	110	118	[illegible]	81	**53**
	RK	**75**	**69**	94	101	[illegible]	138	[illegible]	111	[illegible]
	IW	85	89	79	[illegible]	91	83	101	[illegible]	[illegible]
	LK	96	89	101	126	106	[illegible]	93	101	**53**
Mean		95	91	[illegible]	113	108	118	99	[illegible]	[illegible]
Women	LA	97	[illegible]	105	[illegible]	**123**	117	80	91	51
	AA	92	92	97	91	[illegible]	97	[illegible]	[illegible]	**44**
	IO	110	97	**143**	138	**132**	123	[illegible]	**85**	[illegible]
	KB	88	**71**	87	[illegible]	[illegible]	131	83	[illegible]	**35**
Mean		98	87	108	116	[illegible]	117	88	103	[illegible]

[1] Figures in parentheses are percentages of the respective predicted normal values.

TABLE 4 *Inspiratory and expiratory pressure–flow integrals (l/sec × cm H_2O) determined by planimetry for the flow intervals 0–0.25 and 0–0.50 l/sec, coefficients for the second degree relationships between pressure difference (cm H_2O) across, and flow (l/sec) through, the upper airway, and mean rate of work (kpm/sec) developed during the passage of air through the upper airway at a mean flow of 0.50 l/sec Resting ventilation, 10 men and 5 women with unilateral paralysis of the recurrent nerve Hyperventilation, 10 men and 4 women with unilateral paralysis of the recurrent nerve*

	Inspiration					Expiration				
	0.25 l/sec	0.50 l/sec				0.25 l/sec	0.50 l/sec			
Subject	$\int_0$ l/sec	$\int_0$ l/sec	K_1	K_2	$E_{(0.50)} 10^{-3}$	$\int_0$ l/sec	$\int_0$ l/sec	K_1	K_2	$E_{(0.50)} 10^{-3}$
Resting ventilation					MEN					
RP	0.033	0.147	0.94	0.36	3.63	0.025	0.140	0.48	0.96	3.45
RK	0.052	0.367	0.39	3.82	9.06	0.040	0.528[a]	1.66[c]	8.83	13.03
GL	0.022	0.112	0.51	0.58	2.76	0.010	0.040	0.26	0.19	0.99
FW	0.032	0.179	0.62	1.22	4.42	0.012	0.099	−0.02[c]	1.22	2.44
TA	0.030	0.165	0.60	1.08	4.07	0.042	0.229	0.86	1.46	5.65
FK	0.022	0.077	0.79	−0.26[c]	1.90	0.010	0.045	0.28	0.12	1.11
HJ	0.020	0.102	0.46	0.53	2.52	0.025	0.139	0.48	0.94	3.43
AH	0.008	0.052	0.10	0.48	1.28	0.013	0.087	0.14	0.84	2.15
GAS	0.037	0.197	0.79	1.18	4.86	0.023	0.110	0.59	0.43	2.71
TuA	0.010	0.075	0.04	0.84	1.85	0.007	0.075	0.15[c]	1.13	1.85
Mean	0.027	0.147	0.52	0.98	3.64	0.021	0.150	0.13	1.61	3.68
s d	±0.013	±0.091	±0.29	±1.09	±2.25	±0.013	±0.142	±0.69	±2.57	±3.55
					WOMEN					
SL	0.102	0.616	1.60	4.99	15.20	0.102	0.488	2.62	1.92	12.04
FA	0.077	0.605	0.09	7.13	14.93	0.015	0.095[a]	0.20	0.84	2.34
AA	0.013	0.603	2.07	10.31	14.88	0.102	0.750[a]	0.53	8.21	18.51
LO	0.030	0.212	0.22	2.21	5.23	0.023	0.107	0.62[b]	0.36	2.64
KB	0.057	0.311	1.16	1.99	7.67	0.320	—	−3.49[c]	41.18[b]	—
Mean	0.062	0.469	0.20	5.33	11.58	0.112	0.360	0.10	10.50	8.88
s d	±0.028	±0.193	±1.42	±3.51	±4.77	±0.123	±0.318	±2.22	±17.44	±7.84
Hyperventilation					MEN					
RP	0.037	0.190	0.85	1.01	4.69	0.022	0.140	0.29	1.25	3.45
RK	0.060	0.369	0.89	3.10	9.10	0.050	0.533	1.06	7.99	13.15
GL	0.017	0.087	0.39	0.46	2.15	0.013	0.070	0.27	0.43	1.73
FW	0.017	0.094	0.34	0.62	2.32	0.015	0.072	0.38	0.29	1.78
TA	0.018	0.125	0.15	1.27	3.08	0.020	0.112	0.38	0.77	2.76
FK	0.020	0.109	0.41	0.70	2.69	0.005	0.022	0.14	0.05	0.54
HJ	0.023	0.135	0.39	1.04	3.33	0.027	0.142	0.59	0.82	3.50
AH	0.010	0.070	0.08	0.72	1.73	0.005	0.027	0.10	0.17	0.67
GAS	0.022	0.112	0.51	0.58	2.76	0.010	0.039	0.34	0.05	0.94
TuA	0.015	0.073	0.38	0.31	1.80	0.010	0.063	0.14	0.55	1.55
Mean	0.021	0.136	0.44	0.98	3.37	0.018	0.122	0.16	1.24	3.01
s d	[illegible]	[illegible]	±0.26	±0.80	±2.19	±0.013	±0.151	±0.45	±2.40	±3.72
					WOMEN					
SL	0.105	0.561	2.23	3.38	13.84	0.048	0.357	0.22	3.96	8.81
FA	0.052	0.334	0.66	3.02	8.24	0.015	0.045	0.60	0.36	1.11
AA	0.077	0.274	2.74	0.82	6.76	0.053	0.327	0.78	2.76	8.07
LO	0.037	0.237	0.47	2.14	5.85	0.023	0.115	0.55	0.55	2.84
KB			—	—	—	—	—	—	—	—
Mean	[illegible]	0.351	1.53	1.93	8.67	0.035	0.211	0.54	1.73	5.21
s d	0.030	0.145	±1.13	±3.30	±3.58	±0.019	±0.151	±0.23	±1.98	±3.80

[a] Integrals determined from extrapolated curves.

[b] Coefficients determined from integrals with upper limit less than 0.25 and 0.50 l/sec

[c] In a rigid system negative values for the constants cannot exist It has not been possible so far to decide whether the negative values are due to inaccuracy in the binomial approximation or to a departure from rigidity of the system

31 [illegible]

TABLE 5 *Equations derived from means of coefficients of the second degree relationships between pressure difference (cm H_2O) across, and flow (l/sec) through, the upper airway 10 men and 5 women with unilateral paralysis of the recurrent nerve*

	Resting ventilation		Hyperventilation	
	Inspiration	Expiration	Inspiration	Expiration
Men	$P=0.52\,V+0.98\,V^2$	$P=0.13\,V+1.61\,V^2$	$P=0.44\,V+0.98\,V^2$	$P=0.16\,V+1.24\,V^2$
Women	$P=0.20\,V+5.33\,V^2$	$P=0.10\,V+10.50\,V^2$	$P=1.53\,V+1.93\,V^2$	$P=0.54\,V+1.73\,V^2$

Upper airway resistance

The pressure–flow relationship was curvilinear in all cases and could be represented by second degree polynomials The means for the coefficients of the first degree terms for men and women, inspiration, expiration resting ventilation and hyperventilation covered a range from 0.10 to 1.53 Both these extreme mean values were found in women the former at rest during expiration, the latter during inspiration and hyperventilation The corresponding means for the second degree coefficients for men varied around 1.0, for women the means were 5.33 and 10.50 for inspiration and expiration at rest, and 1.93 and 1.73 during hyperventilation (Table 5) The mean rate of work for a mean flow of 0.5 l/sec was about 0.003 kpm/sec for men for women the means varied between 0.005 and 0.012 kpm/sec (Table 4) Mean pressure differences for inspiration and expiration at rest and during hyperventilation for flow rates of 0.25 and 0.50 l/sec, and during hyperventilation also 1.00 l/sec were of the same magnitude in male patients and normal men The mean pressure drops were 0.15, 0.46 and 1.41 cm H_2O

TABLE 6 *Means and standard deviations of inspiratory and expiratory pressure differences (cm H_2O) across the upper airway during resting ventilation, at flow rates of 0.25 and 0.50 l sec, compared with normal values (Schiratzki, 1964) 10 men and 5 women with unilateral paralysis of the recurrent nerve*

Flow rate (l/sec)	Men				Women			
	Inspiration		Expiration		Inspiration		Expiration	
	Normal	Unilat	Normal	Unilat	Normal	Unilat	Normal	Unilat
0.25	0.19 ±0.08	0.19 +0.03	0.16 ±0.08	0.13 +0.08	0.16 +0.07	0.38 +0.23	0.12 ±0.05	0.68 ±0.61
0.50	0.57 +0.42	0.51 +0.28	0.46 +0.29	0.47 ±0.37	0.53 ±0.21	1.43 +0.56	0.51 ±0.27	2.67 ±3.40

TABLE 7. *Means and standard deviations of inspiratory and expiratory pressure differences (cm H_2O) across the upper airway during hyperventilation, at flow rates of 0.25, 0.50 and 1.00 l/sec, compared with normal values (Schiratzki 1964). 10 men and 4 women with unilateral paralysis of the recurrent nerve*

Flow rate (l/sec)	Men				Women			
	Inspiration		Expiration		Inspiration		Expiration	
	Normal	Unilat	Normal	Unilat	Normal	Unilat	Normal	Unilat
0.25	0.19 ±0.12	0.17 ±0.10	0.14 ±0.09	0.12 +0.06	0.17 ±0.09	0.50 ±0.24	0.08 ±0.04	0.24 ±0.11
0.50	0.44 ±0.31	0.47 ±0.30	0.39 ±0.25	0.39 +0.41	0.48 +0.18	1.25 ±0.51	0.24 ±0.20	0.70 ±0.46
1.00	1.14 +0.91	1.42 ±0.97	1.22 ±0.87	1.39 ±2.00	1.52 +0.50	3.46 ±1.61	0.84 ±0.90	2.27 ±1.89

They were considerably higher for female patients than normal women the values were 0.45, 1.51 and 2.87 cm H_2O (Tables 6 and 7). The upper airway resistance for men calculated from the pressure drop for a flow rate of 0.5 l/sec was 1.02 and 0.94 cm H_2O/l/sec at rest for inspiration and expiration respectively and 0.94 and 0.78 cm H_2O/l/sec during hyperventilation. For women the corresponding values were 2.86 and 3.34 cm H_2O/l/sec at rest and 2.50 and 1.40 cm H_2O/l/sec during hyperventilation. There was a considerable dispersion within the groups and a much steeper rise of the pressure flow curves for women than for men (Fig. 1).

Comparison of upper airway resistance by means of the pressure flow integrals gave the following results. The pressure flow integrals were larger for *female* cases than for *male* ones. The differences were *significant during* inspiration for the intervals 0–0.25 and 0–0.50 l/sec during resting ventilation ($P < 0.01$ and $P < 0.001$) and hyperventilation ($P < 0.01$). For expiration the difference was almost significant or not significant up to 0.50 l/sec (Fig. 2).

In Fig. 3 the equations in Table 5 are plotted; the expiratory curves have *been transferred from the third to the first quadrant to facilitate the analysis.* The *inspiratory* pressure flow integrals were larger than the *expiratory* ones. The differences were not significant except for hyperventilation in the smaller flow interval for both men and women where the difference was almost significant ($P < 0.05$). Only during resting ventilation for the flow intervals 0–0.50 and 0–0.25 l/sec for men and women respectively did the expiratory integrals exceed the inspiratory ones. The integrals were larger at *rest* than during *hyperventilation* except for women during inspiration in the smaller flow interval but for neither sex was the difference statistically significant (Fig. 4).

For the comparison of normals and cases of paralysis of the recurrent nerve the normal values were obtained in an earlier study (Schiratzki 1964).

As might well be expected from Fig. 5 no difference between *normal men*

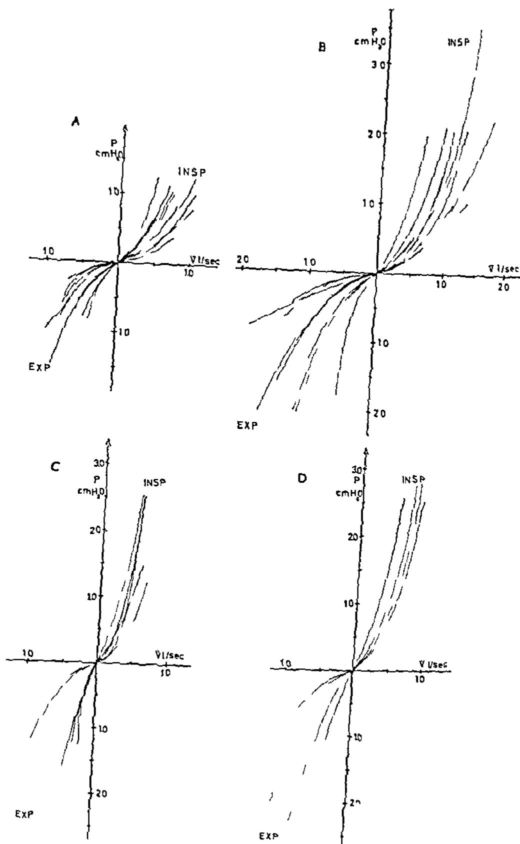


FIG. 1. Relationship between pressure difference (cm H_2O) across (*ordinates*) and flow (l/sec) through (*abscissae*) the upper airway in cases of unilateral paralysis of the recurrent nerve. (A) Men, resting ventilation. (B) Men, hyperventilation. (C) Women, resting ventilation. (D) Women, hyperventilation.

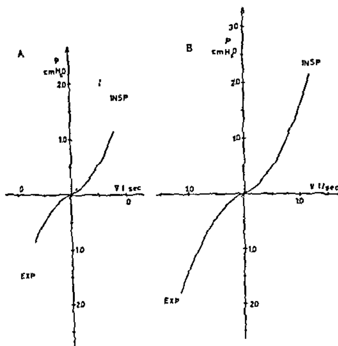


Fig 2 Comparison between male (*continuous lines*) and female (*broken lines*) cases of unilateral paralysis of the recurrent nerve (A) Resting ventilation (B) Hyperventilation Curves constructed from mean equations Dimensions of variables as in Fig 1

and *male patients* was found as regards the pressure flow integrals The larger integrals found in *female patients* than in *normal women* (Fig 6) corresponded to statistically different integrals for inspiration both at rest and during hyperventilation (P 0 01 0 001) For expiration the difference was almost significant but only at rest and during hyperventilation for flow rates from 0 0 25 l/sec ($P<0\ 05$)

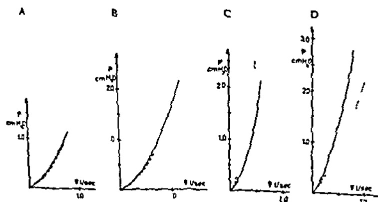


Fig 3 Comparison between inspiration (*continuous lines*) and expiration (*broken lines*) in cases of unilateral paralysis of the recurrent nerve (A) Men resting ventilation (B) Men hyperventilation (C) Women resting ventilation (D) Women hyperventilation Curves constructed from mean equations Dimensions of variables as in Fig 1

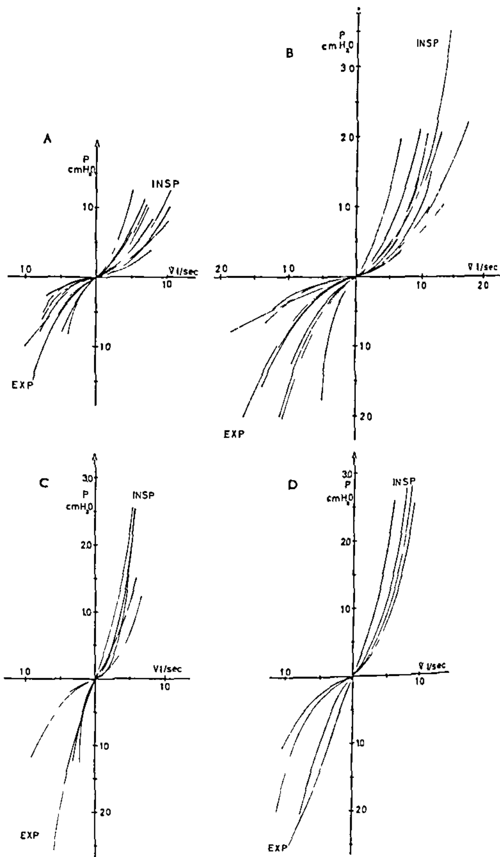


FIG 1 Relationship between pressure difference, cm H_2O, across (*ordinates*) and flow, l sec, through (*abscissae*) the upper airway in cases of unilateral paralysis of the recurrent nerve (A) Men, resting ventilation (B) Men, hyperventilation (C) Women, resting ventilation (D) Women, hyperventilation

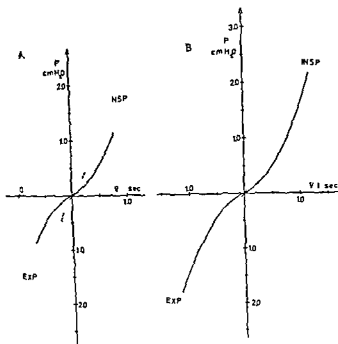


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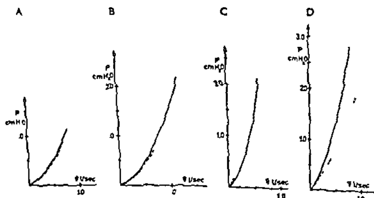


Fig 3 Comparison between inspiration (*continuous lines*) and expiration (*broken lines*) in cases of unilateral paralysis of the recurrent nerve (A) Men resting ventilation (B) Men hyperventilation (C) Women resting ventilation (D) Women *hyperventilation* Curves constructed from mean equations Dimensions of variables as in Fig 1

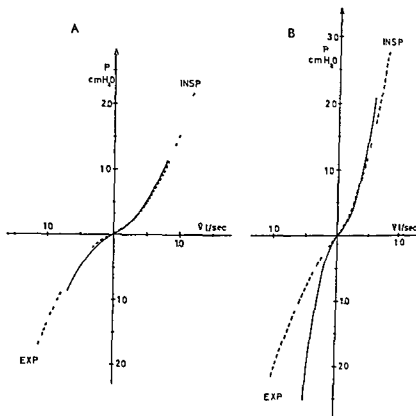


Fig 4 Comparison between resting ventilation (*continuous lines*) and hyperventilation (*broken lines*) in cases of unilateral paralysis of the recurrent nerve (A) Men (B) Women Curves constructed from mean equations Dimensions of variables as in Fig 1

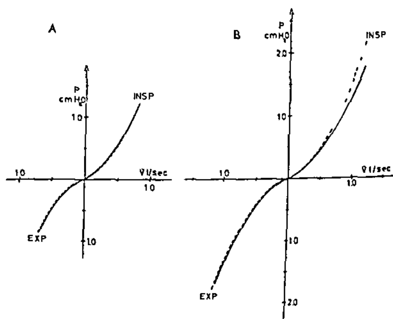


Fig 5 Comparison between normal men (*continuous lines*) and male cases of unilateral paralysis of the recurrent nerve (*broken lines*) (A) Resting ventilation (B) Hyperventilation Curves constructed from mean equations Dimensions of variables as in Fig 1

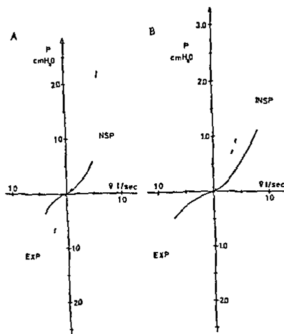


Fig 6 Comparison between normal women (*continuous lines*) and female cases of unilateral paralysis of the recurrent nerve (*broken lines*) (A) Resting ventilation (B) Hyperventilation Curves constructed from mean equations Dimensions of variables as in Fig 1

Upper respiratory mechanical work

The mechanical work done in moving the ventilatory air through the upper airway is presented in Table 8 The mean values were 0.009 and 0.028 kpm/l of $\dot{V}_E$ for men and women respectively the difference between

Table 8 *Mechanical work W (kpm/l of V_E) performed in forcing respiratory air through the upper airway during resting ventilation 10 men and 4 women with unilateral paralysis of the recurrent nerve*

Men			Women		
Subject	W	Tidal volume	Subject	W	Tidal volume
RI	0.009	0.6	SL	0.030	0.8
RK	0.008	0.8	IA	0.018	0.7
GI	0.004	0.[illegible]	AA	0.021	0.5
FW	0.006	0.9	IO	0.014	0.9
FA	0.011	0.8	KB	—	—
IK	0.005	0.8			
HJ	0.016	0			
AH	0.003	0.8			
CVS	0.010	0.7			
TuA	0.013	1.1			
Mean	0.009	0.8		0.028	0.7
S.D.	0.004	±0.1		±0.007	±0.2

these two values was significant ($P<0.001$). Between the male patients and normal men no difference was found. There was a significant difference between female patients and normal women ($P<0.001$).

Bilateral Paralysis of the Recurrent Nerve

Spirometry

In this group 3 of 10 patients were examined by spirometry. The results of this examination are presented in Table 9. One patient showed a low VC (44 %)[1], high FRC (139 %) and RV (225 %) and high quotients FRC/TLC (152 %) and RV/TLC (211 %). The results of the static spirometry for the 2 other patients were normal.

$FEV_{1.0}$ was subnormal for 2 patients (41 and 53 %). For these patients FEV % was also abnormal (80 and 70 %, respectively). One patient was incapable of performing the MVV_F test, and for the two others it resulted in values far below the normal range (19 and 30 %, respectively).

TABLE 9. *Total lung capacity (TLC), vital capacity (VC), functional residual capacity (FRC), residual volume (RV), functional residual (FRC/TLC) and residual quotients (RV/TLC), forced expiratory volume in one second, expressed in absolute values ($FEV_{1.0}$) and in relation to forced vital capacity (FEV %), and maximum voluntary ventilation at a free rate (MVV_F). 3 women with bilateral paralysis of the recurrent nerve*

All values expressed as a percentage of predicted values. Values outside twice the standard deviation are in bold face.

Subject	TLC	VC	FRC	RV	FRC/TLC	RV/TLC	$FEV_{1.0}$	FEV %	MVV_F
EdW	104	**44**	**139**	**225**	**153**	**211**	**41**	**80**	—
IS	93	92	86	90	98	104	93	103	**19**
IW	85	79	110	99	98	113	**53**	**70**	**30**
Mean	94	72	112	138	116	143	62	84	25

Upper airway resistance

There are two conspicuous features in the bilateral paralysis group. A flow of 0.5 l/sec was attained in only 8 of 20 experiments and the curves

[1] Figures in parentheses are percentages of the respective predicted normal values.

FIG. 7. Relationship between pressure difference across (*ordinates*) and flow through (*abscissae*) the upper airway in cases of bilateral paralysis of the recurrent nerve during resting ventilation. Dimensions of variables as in Fig. 1.

FIG. 8. Comparison between inspiration (*continuous lines*) and expiration (*broken lines*) in cases of bilateral paralysis of the recurrent nerve during resting ventilation. Curves constructed from mean equations. Dimensions of variables as in Fig. 1.

FIG. 9. Comparison between normal women (*dotted lines*), female cases of unilateral paralysis of the recurrent nerve (*broken lines*) and cases of bilateral paralysis (*continuous lines*). Curves constructed from mean equations. Dimensions of variables as in Fig. 1.

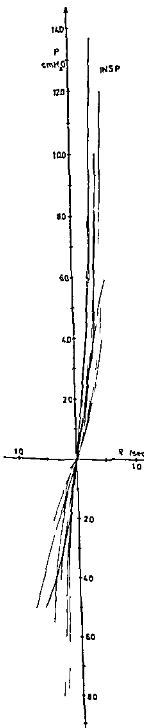


Fig 7

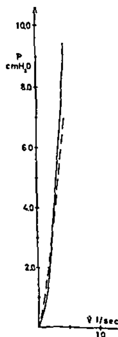


Fig 8

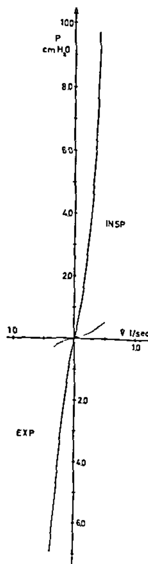


Fig 9

TABLE 10 *Inspiratory and expiratory pressure–flow integrals (l/sec × cm H_2O) determined by planimetry for the flow intervals 0–0.25 and 0–0.50 l/sec, coefficients for the second degree relationships between pressure difference (cm H_2O) across, and flow (l/sec) through, the upper airway, and mean rate of work (kpm/sec) developed during the passage of air through the upper airway at a mean flow of 0.50 l/sec One man and 9 women with bilateral paralysis of the recurrent nerve*

	Inspiration					Expiration				
Subject	$\int_{0\,l/sec}^{0.25\,l/sec}$	$\int_{0\,l/sec}^{0.50\,l/sec}$	K_1	K_2	$\Gamma_{(0.50)}10^{-3}$	$\int_{0\,l/sec}^{0.25\,l/sec}$	$\int_{0\,l/sec}^{0.50\,l/sec}$	K_1	K_2	$E_{0.50}10^{-3}$
I dW	0.333	—	1.90[b]	26.27[b]	—	0.759	—	20.18[b]	11.42[b]	—
LC*	0.982	—	−8.62[b,c]	120.13[b]	—	0.106	—	4.67[b]	24.97[b]	—
FsW	0.476	3.303	−0.44[c]	40.30	81.50	0.176	0.746	5.30	1.01	18.41
GS	0.799	—	21.96[b]	10.82[b]	—	—	—	31.65[b]	−16.88[b,c]	—
IS	0.226	1.965[a]	−1.26[c]	25.46	48.48	0.146	0.616[a]	1.42	0.77	15.21
IW	0.210	1.462[a]	1.74	14.93	36.07	0.103	0.683	1.13	6.50	16.85
ND	0.340	1.242	11.82	−2.83[c]	30.65	0.306	0.892	12.45	7.97	22.01
KF	—	—	0.94[b]	106.31[b]	—	0.280	—	0.69[b]	24.81[b]	—
LJ	0.273	2.794[a]	−4.88[c]	40.85	68.94	0.203	1.199[a]	3.40	9.29	29.58
AA	0.996	—	5.42[b]	79.36[b]	—	1.259[a]	—	18.81[b]	64.43[b]	—
Mean	0.507	2.153	2.86	46.16	53.13	0.404	0.827	10.30	13.45	20.41
S D	±0.324	±0.877	±8.67	±41.77	±21.64	±0.376	±0.232	±10.29	±21.64	±5.71

[a] Integrals determined from extrapolated curves
[b] Coefficients determined from integrals with upper limit less than 0.25 and 0.50 l/sec
[c] Regarding negative values for the coefficients see note to Table 4

were considerably steeper than those of the unilateral and normal groups (Figs 7 and 9) Nonetheless, second degree polynomials could be fitted to the curves, although one of them deviated in shape to some extent Moreover, for this group the dispersion was large The coefficients of the second degree polynomials, the pressure–flow integrals and mean rate of work for a mean flow of 0.50 l/sec are given in Table 10 The mean equations for inspiration and expiration were respectively $P = 2.86\ V + 46.16\ V^2$ and $P = 10.30\ V + 13.45\ V^2$

The mean pressure differences at flow rates of 0.25 and 0.50 l/sec are presented in Table 11, together with the corresponding values for normal women and female cases of unilateral cord paralysis The ratio between the pressure drops for normal women and the cases of unilateral and bilateral paralysis was of the order 1 2 20 during both inspiration and expiration The upper airway resistance calculated from the pressure drop at a flow of 0.50 l/sec was 25.88 and 17.02 cm H_2O/l/sec for inspiration and expiration, respectively

The pressure–flow integral could not be determined in one case during

TABLE 11 *Means and standard deviations of inspiratory and expiratory pressure differences (cm H_2O) across the upper airway, at a flow rate of 0 25 and 0 50 l/sec, compared with normal values (Schiratzki, 1964) and the values for female cases of unilateral paralysis One man and 9 women with bilateral paralysis of the recurrent nerve*

Flow rate (l sec)	Inspiration			Expiration		
	Normal	Unilateral	Bilateral	Normal	Unilateral	Bilateral
0 25	0 16	0 38	3 60	0 12	0 68	3 42
	+0 07	±0 23	±2 30	±0 08	±0 64	±2 79
0 50	0 53	1 43	12 94	0 51	2 67	8 51
	±0 21	±0 56	±8 87	±0 27	±3 40	±7 10

inspiration and in another during expiration in the flow range 0–0 25 l/sec for 5 subjects it could not be determined in the range 0–0 50 l/sec in either respiratory phase The comparison of *inspiratory* and *expiratory* integrals was thus performed with 8 and 5 cases in the smaller and larger flow ranges, respectively The integrals were larger for inspiration than for expiration The difference was not significant in the smaller and almost significant in the greater flow interval ($P<0.05$) (Fig 8)

The integrals for the *cases of bilateral cord paralysis* were about 20 times larger than for *normal women* in the flow interval 0 0 25 l/sec The dif

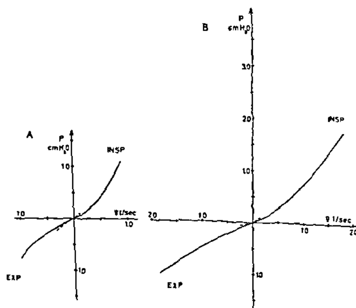


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TABLE 10. *Inspiratory and expiratory pressure–flow integrals (l/sec · cm H_2O) determined by planimetry for the flow intervals 0–0.25 and 0–0.50 l/sec, coefficients for the second degree relationships between pressure difference (cm H_2O) across and flow (l/sec) through the upper airway, and mean rate of work (kpm/sec) developed during the passage of air through the upper airway at a mean flow of 0.50 l/sec. One man and 9 women with bilateral paralysis of the recurrent nerve*

	Inspiration					Expiration				
	$\int_{0\ l/sec}^{0.25\ l/sec}$	$\int_{0\ l/sec}^{0.50\ l/sec}$				$\int_{0\ l/sec}^{0.25\ l/sec}$	$\int_{0\ l/sec}^{0.50\ l/sec}$			
Subject			k_1	k_2	$F_{0.50} \cdot 10^{-3}$			k_1	k_2	$F_{0.50} \cdot 10^{-3}$
LdW	0.133	—	1.90[b]	26.27[b]	—	0.7[illegible]9	—	20.48[b]	11.4[illegible][b]	—
LI	0.952	—	−8.62[b][c]	120.13[b]	—	0.406	—	4.6[illegible][b]	24.9[illegible][b]	—
LsW	0.4[illegible]6	3.303	−0.44[c]	40.30	81.50	0.176	0.746	5.30	1.01	18.11
CS	0.799	—	21.96[b]	10.82[b]	—	—	—	31.65[b]	−16.88[b]	—
IS	0.226	1.965[a]	−1.26[c]	25.46	48.48	0.146	0.616[a]	4.42	0.77	15.9[illegible]
IW	0.210	1.162[a]	1.74	14.93	36.07	0.103	0.683	1.13	0.70	16.85
ND	0.310	1.249	11.82	−2.83[c]	30.65	0.306	0.892	12.45	7.97	9.[illegible]1
KF	—	—	0.94[b]	106.31[b]	—	0.280	—	0.69[b]	24.81[b]	—
LJ	0.273	2.794[a]	−4.88[c]	40.85	68.94	0.203	1.199[a]	3.40	9.29	29.58
AA	0.996	—	5.42[b]	79.36[b]	—	1.259[a]	—	18.81[b]	64.43[b]	—
Mean	0.507	2.153	2.86	46.16	53.13	0.404	0.897	10.30	13.45	[illegible]41
S.D.	±0.3[illegible]4	±0.877	±8.67	±41.77	±21.64	±0.376	±0.232	±10.29	±21.64	±5.71

[a] Integrals determined from extrapolated curves

[b] Coefficients determined from integrals with upper limit less than 0.25 and 0.50 l/sec

[c] Regarding negative values for the coefficients see note to Table 4

were considerably steeper than those of the unilateral and normal groups (Figs. 7 and 9). Nonetheless second degree polynomials could be fitted to the curves although one of them deviated in shape to some extent. Moreover for this group the dispersion was large. The coefficients of the second degree polynomials, the pressure flow integrals and mean rate of work for a mean flow of 0.50 l/sec are given in Table 10. The mean equations for inspiration and expiration were respectively $P = 2.86\ \dot{V} + 46.16\ \dot{V}^2$ and $P = 10.30\ \dot{V} + 13.45\ \dot{V}^2$.

The mean pressure differences at flow rates of 0.25 and 0.50 l/sec are presented in Table 11 together with the corresponding values for normal women and female cases of unilateral cord paralysis. The ratio between the pressure drops for normal women and the cases of unilateral and bilateral paralysis was of the order 1 : 2 : 20 during both inspiration and expiration. The upper airway resistance calculated from the pressure drop at a flow of 0.50 l/sec was 25.88 and 17.02 cm H_2O/l/sec for inspiration and expiration respectively.

The pressure flow integral could not be determined in one case during

One of the 3 examined cases of bilateral paralysis had a higher ventilatory mid position For all 3 dynamic spirometry indicated pathologic conditions

The MVV_F test was the only one that yielded abnormal or near abnormal results in all patients It is interesting to notice that even in the male group where the direct measurement of resistance failed to disclose any impairment this examination seemed to be sensitive enough to disclose even minor defects

The value of testing the maximum breathing capacity has been emphasized by Carlens (1954) who found low values in cases of bilateral paralysis of the recurrent nerve After surgical restoration of the airway the values improved Grimby & Soderholm (1963) have reported pathologic values of MVV_F in cases of vocal cord paralysis Although the examination of maximum breathing capacity appears to be a good screening test of patients with laryngeal obstruction abnormal findings may also be due to lung and chest diseases

Upper airway resistance

Except for the minor modification required for measuring the subglottic pressure in the tracheotomized patients the method has been described and discussed in an earlier paper (Schiratzki 1964) To examine the validity of the equations for the present material the calculated pressure drops for flow rates of 0 25 and 0 50 l/sec were compared with the observed values For cases of unilateral paralysis the coefficients of variation for the difference between calculated and observed values were 23 and 8 % respectively For 0 25 l/sec the observed values were higher (almost significant $P < 0.05$) for 0 50 l/sec no difference was found For the bilateral cases and a flow of 0 25 l/sec the difference between calculated and observed values gave a coefficient of variation of 8 % There was no statistical difference As only a few patients attained a flow of 0 50 l/sec no comparison was made at this level In the normal material the comparison of calculated and observed values gave a coefficient of variation of 16 and 5 % at the smaller and larger flow levels respectively (Schiratzki 1964) This suggests that the validity of the equations in the present material might be poorer than in the normal series

It would be expected that in the midline position of the vocal cord the area open for the passage of air would be smaller even in the unilateral state and thus give rise to an increase in resistance It has also been suggested that a change in aerodynamic configuration caused by the protruding cord would increase the turbulent flow component (Berendes 1956) The fact that male cases of unilateral paralysis of the recurrent nerve presented normal values suggests the presence of a critical cross sectional area and/or a compensatory abduction of the mobile cord The signs of increased upper airway resistance found in the female group may be accounted for by an insufficient compensatory abduction of the cord and/or the cross sectional area being below the critical area owing to smaller dimension of the female airway

TABLE 12 *Mechanical work, W (kpm/l of $\dot{V}_E$) performed in forcing respiratory air through the upper airway during resting ventilation One man and 9 women with bilateral paralysis of the recurrent nerve*

Subject	W	Tidal volume
EdW	0 080	0 6
LL	0 133	0 5
EsW	0 104	0 5
GS	0 104	0 3
IS	0 016	0 6
IW	0 032	0 6
ND	0 094	1 2
KF	0 030	0 5
IJ	0 060	0 7
AV	0 053	0 3
Mean	0 074	0 6
S D	±0 035	±0 3

ferences were significant for both inspiration and expiration ($P<0\ 001$ and $P<0\ 05$ respectively) For 0 0 50 l/sec they were smaller but still significant ($P<0\ 001$) (Fig 9)

The pressure–flow integrals for the *bilateral group* were larger than the corresponding ones for the group of *women with unilateral* cord paralysis (Fig 9) For both flow ranges the differences were significant during inspiration ($P<0\ 05$ and $P<0\ 01$) During expiration the differences were significant only for the range 0 0 50 l/sec ($P<0\ 05$)

Upper respiratory mechanical work

The mean mechanical work performed in displacing the respiratory air through the upper airway was 0 074 kpm/l of $\dot{V}_E$ (Table 12) This value was significantly larger than that for the normal women ($P<0\ 001$) The difference between patients with bilateral and female patients with unilateral cord paralysis was almost significant ($P<0\ 05$)

DISCUSSION

Spirometry

Except for high FRC and RV in one patient and low FIC and VC in another the only abnormal feature in the group of male unilateral patients was the presence of low or even subnormal values of MVV_F In 2 women there was evidence of a higher ventilatory mid position In the presence of normal FIC an increase in the quotient FRC/FIC was regarded as a sign of this especially *in one of the cases where FRC also was increased* In this group the MVV_F values were low and in two cases even abnormal

One of the 3 examined cases of bilateral paralysis had a higher ventilatory mid position. For all 3 dynamic spirometry indicated pathologic conditions. The MVV_F test was the only one that yielded abnormal or near abnormal results in all patients. It is interesting to notice that even in the male group where the direct measurement of resistance failed to disclose any impairment this examination seemed to be sensitive enough to disclose even minor defects.

The value of testing the maximum breathing capacity has been emphasized by Carlens (1954) who found low values in cases of bilateral paralysis of the recurrent nerve. After surgical restoration of the airway the values improved. Grimby & Soderholm (1963) have reported pathologic values of MVV_F in cases of vocal cord paralysis. Although the examination of maximum breathing capacity appears to be a good screening test of patients with laryngeal obstruction, abnormal findings may also be due to lung and chest diseases.

Upper airway resistance

Except for the minor modification required for measuring the subglottic pressure in the tracheotomized patients the method has been described and discussed in an earlier paper (Schiratzki 1964). To examine the validity of the equations for the present material the calculated pressure drops for flow rates of 0.25 and 0.50 l/sec were compared with the observed values. For cases of unilateral paralysis the coefficients of variation for the difference between calculated and observed values were 23 and 8 %, respectively. For 0.25 l/sec the observed values were higher (almost significant $P<0.05$), for 0.50 l/sec no difference was found. For the bilateral cases and a flow of 0.25 l/sec the difference between calculated and observed values gave a coefficient of variation of 8 %. There was no statistical difference. As only a few patients attained a flow of 0.50 l/sec no comparison was made at this level. In the normal material the comparison of calculated and observed values gave a coefficient of variation of 16 and 5 % at the smaller and larger flow levels respectively (Schiratzki 1964). This suggests that the validity of the equations in the present material might be poorer than in the normal series.

It would be expected that in the midline position of the vocal cord the area open for the passage of air would be smaller even in the unilateral state and thus give rise to an increase in resistance. It has also been suggested that a change in aerodynamic configuration caused by the protruding cord would increase the turbulent flow component (Berendes 1956). The fact that male cases of unilateral paralysis of the recurrent nerve presented normal values suggests the presence of a critical cross sectional area and/or a compensatory abduction of the mobile cord. The signs of increased upper airway resistance found in the female group may be accounted for by an insufficient compensatory abduction of the cord and/or the cross sectional area being below the critical area owing to smaller dimension of the female airway.

One man was examined before and after unilateral paralysis of the cord due to a neck operation. At rest only a small difference was found. During hyperventilation the post-operative curve tended towards higher resistance values, especially at high flow rates (Fig. 10).

The observed subnormal values of MVV_F, a maximum performance test, bear out Berendes' (1956) view that impaired ventilation can occur during severe exercise even in cases of unilateral paralysis of the recurrent nerve. The upper airway resistance test failed to reveal any signs of impaired respiratory mechanics in men even during hyperventilation, but it should be remembered that the hyperventilation was far from the maximum. In women the resistance values that were pathologic at rest were not higher during hyperventilation, probably because the increase of the flow rate was not pronounced (Fig. 1). In the female group the pressure-flow curve during resting ventilation indicates a higher resistance during expiration than during inspiration (Fig. 3C). Also the mean pressure drop for a flow of 0.5 l/sec was higher during expiration than during inspiration, but the mean integrals were higher for inspiration than for expiration. One of the expiratory pressure-flow curves was extremely steep and no integral for the flow interval of 0–0.50 l/sec could be obtained. If this highly deviating curve and the pressure drop calculated from it are excluded, then the expiratory resistance will be 2.42 cm H_2O/l/sec instead of 5.34 and the expiratory mean curve will move below the inspiratory curve.

In the group of female patients with unilateral paralysis of the recurrent nerve a mean pressure drop at a flow of 0.50 l/sec yielded a mean upper airway resistance of 4.1 cm H_2O/l/sec at rest and 2.0 during hyperventilation. For the group of patients with bilateral paralysis the value was 21.5. With a technique similar to that in the present investigation Isshiki & von Leden (1964) found values of glottic resistance during whispering of 13–35 acoustic ohm (1 acoustic ohm = 1.02 cm H_2O/l/sec). The glottic opening is then approximately comparable to that in bilateral cases during respiration, implying an acceptable similarity of the results. Examining 30 patients with respiratory diseases by a plethysmographic method DuBois, Botelho & Comroe (1956) found total airway resistance values ranging from 0.6 to 10.8 cm H_2O/l/sec; a patient with glottic stenosis recorded a value of 7.2 cm H_2O/l/sec. The values for the female patients are thus of the same general order as those found in the above material, where the majority of patients displayed dyspnoea on exertion.

The values found in the group with bilateral paralysis were considerably higher and were thus consistent with their clinical symptoms, which in [illegible] cases were so severe as to indicate a tracheostomy.

Work of breathing

Of the observed values in male and female cases of unilateral paralysis, namely 0.009 and 0.028 1pm/l of $\bar{I}_E$, the former was of the same order as in normals, whereas the latter was four times higher. In bilateral paralysis

the value of 0 074 kpm/l of $\dot{V}_E$ was ten times the normal In the normal subject 1 3 % of the oxygen consumption at rest is accounted for by the respiratory muscles (Campbell 1958) Assuming the same efficiency of these muscles in cases of cord paralysis as in normal subjects this would imply an increase in the oxygen consumption of the respiratory muscles of 25 50 % depending on the value chosen for the total work of breathing (Otis 1954 Cherniack & Cherniack, 1961)

ZUSAMMENFASSUNG

Der Stromungswiderstand in den oberen Luftwegen — Subglottis bis Mundoff nung — gemessen als Beziehung von Druckabfall in und Strömungsgeschwindig keit durch die oberen Luftwege wurde bei 10 Mannern und 5 Frauen mit ein seitiger und bei einem Mann und 9 Frauen mit beiderseitiger Recurrenslahmung bestimmt

Die Beziehung zwischen Druckabfall und Stromungsgeschwindigkeit war bei In wie Exspiration und bei Ruheatmung wie Hyperventilation kurvenlinear Alle Kurven konnen als Gleichungen zweiten Grades ausgedruckt werden

Der mittlere Stromungswiderstand der oberen Luftwege bei Mannern mit ein seitiger Recurrenslahmung betrug wahrend Ruheatmung und Hyperventilation bei einer Stromungsgeschwindigkeit von 0 5 l/sec 1 0 bzw 0 9 cm H O/l/sec Die entsprechenden Werte fur Frauen waren 4 1 und 2 0 cm H_O/l sec

Bei Fallen mit beiderseitiger Recurrenslahmung betrug der mittlere Stromungs widerstand bei einer Stromungsgeschwindigkeit von 0 5 l/sec 21 5 cm H_O/l/sec wahrend Ruheatmung

Die mechanische Arbeit die Luft durch die oberen Atemwege zu befordern wurde als Produkt des Atemvolumens und des Druckabfalls berechnet Wahrend Ruheatmung hatte sie bei Mannern und Frauen mit einseitiger Recurrenslahmung einen mittleren Wert von 0 009 bzw 0 024 kpm l $\dot{V}_E$ Bei Fallen mit beiderseitiger Lahmung betrug sie 0 074 kpm l $\dot{V}_E$ Acht Falle mit einseitiger und 3 mit beider seitiger Recurrenslahmung wurden unter Anwendung statischer und dynamischer Spirometrie untersucht Alle zeigten subnormale MVV$_E$ Werte

REFERENCES

BERENDES J 1956 Neuere Ergebnisse über Bewegungsstörungen des Kehlkopfes *Arch Ohr Nas Kehlkopfheilk* *169* 1

BERGLUND E BIRATH G BJURE J GRIMBY G KJELLMER I SANDQVIST L and SODERHOLM B 1963 Spirometric studies in normal subjects Forced expirograms in subjects between and 70 years of age *Acta Med Scand* *173* 18

BERNSTEIN L D SILVA J L and MENDEL, D 1952 The effect of the rate of breathing on the maximum breathing capacity determined with a new spirometer *Thorax* *7* 255

CAMPBELL E J M 1958 *The Respiratory Muscle and the Mechanics of Breathing* p 83 Lloyd Luke London

CARLENS E 19 4 Bilateral abductor paralysis of the larynx Medical and surgical aspects *Acta Otolaryng* (Stockh) Suppl *118* 57

CHERNIACK R M and CHERNIACK L 19 1 *Respiration in Health and Disease* p 28 Saunders Philadelphia

DuBois, A. B., Botelho, S. Y., and Comroe, J. H., 1956. A new method for measuring airway resistance in man using a body plethysmograph. Values in normal subjects and in patients with respiratory disease. *J. Clin. Invest.*, *35*, 327.

Ferris, B. G. Jr., Opie, L. and Mead, J., 1960. Partitioning of respiratory resistance in man. *Fed. Proc.*, *19*, 377.

Grimby, G., and Soderholm, B., 1963. *Spirometric studies in normal man. Static lung volumes and maximum voluntary ventilation in adults with a note on physical fitness. Acta Med. Scand.*, *173*, 199.

Holmgren, A., 1954. Determination of the functional residual volume by means of the helium dilution method. *Scand. J. Clin. Lab. Invest.*, *6*, 131.

Hyatt, R. E., and Wilcox, R. E., 1961. Extrathoracic airway resistance in man. *J. Appl. Physiol.*, *16*, 326.

Isshiki, N., and von Leden, H., 1964. Hoarseness. Aerodynamic Studies. *Arch. Otolaryng.* (Chic.) *80*, 206.

Jackson, Ch., and Jackson, Ch. L., 1959. *Diseases of the Nose, Throat and Ear.* p. 655. Saunders, Philadelphia.

Otis, A. B., 1954. The work of breathing. *Physiol. Rev.*, *34*, 449.

Pappenheimer, J., *et al.*, 1950. Standardization of definitions and symbols in respiratory physiology. *Fed. Proc.* 9, 602.

Schiratzki, H., 1964. Upper airway resistance in normal man during mouth breathing. *Acta Otolaryng.* (Stockh.) *58*, 535.

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THE FUNCTION OF THE CRICOPHARYNGEAL SPHINCTER DURING SWALLOWING

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From the Department of Otolaryngology, The Radcliffe Infirmary and the Nuffield Institute for Medical Research, Oxford

Experimental work in the dog and cineradiography of swallowing in man (at 25 frames/sec) has been performed in order to study the changes that occur in the cricopharyngeal sphincter during swallowing. It has been shown that the sphincter in the normal closed state provides a zone of elevated pressure which prevents the reflux of oesophageal contents into the pharynx. This resting condition is seen to alter in the dog during a reflexly induced swallow, when the sphincter first relaxes and then contracts. These actions are dependent on at least one of the nerves to the cricopharyngeus muscles being intact and in continuity between the pharynx above and the sphincter below. The bolus on reaching the relaxed sphincter is able to pass through under the action of gravity and thrust from the tongue above. Cine films do not show that movement of the cricoid forwards opens the sphincter ahead of the bolus.

The cricopharyngeal sphincter during swallowing has been investigated by many workers.

Schreiber (1904) considered that elevation and forward movement of the larynx draws up the oesophagus and opens the sphincter.

Barclay (1936) maintained that negative pressure in the pharynx *sucks* the food down, the sphincter actively dilating to allow it to pass.

Negus (1949) stated that in certain animals including the *dog*, the top of the oesophagus is opened by the cartilages of Santorini rotating forwards, and that this occurred since the oesophagus is not only attached to the back of the cricoid but also to these cartilages. *He thought that this* mechanism was inefficient in man.

Lerche (1950) considered that contraction of the middle constrictors and the marked pressure thus created, overcame the contraction of the cricopharyngeus muscles and opened the sphincter.

Intraluminal pressure measurements by Fyke & Code (1955) indicated that there was a fall of pressure in the sphincter denoting relaxation which precedes the pharyngeal constrictor wave.

Ardran & Kemp (1955, 1961) using *cineradiography* have shown that in

DuBois, A B, Botelho, S Y, and Comroe, J H, 1956 A new method for measuring airway resistance in man using a body plethysmograph Values in normal subjects and in patients with respiratory disease *J Clin Invest*, *35*, 327

Ferris, B G Jr, Opie, L, and Mead, J, 1960 Partitioning of respiratory resistance in man *Fed Proc*, *19*, 377

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Holmgren, A, 1954 Determination of the functional residual volume by means of the helium dilution method *Scand J Clin Lab Invest*, *6*, 131

Hyatt, R E, and Wilcox, R E, 1961 Extrathoracic airway resistance in man *J Appl Physiol*, *16*, 326

Isshiki, N, and Ledfn, H v, 1964 Hoarseness Aerodynamic Studies *Arch Otolaryng* (Chic) *80*, 206

Jackson, Ch, and Jackson, Ch I, 1959 *Diseases of the Nose, Throat and Ear*, p 653 Saunders Philadelphia

Otis A B, 1954 The work of breathing *Physiol Rev* *34*, 449

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the erect position, the bolus passes into the upper oesophagus by means of thrust from the tongue assisted by gravity. The pharynx is then cleared of its contents by a peristaltic muscular contraction which passes downwards in a smooth fashion involving the sphincter as it does so.

Dohlman & Mattsson (1959) considered that the sphincter is opened by the cricoid cartilage moving forwards, the posterior part of the sphincter ring of muscle being fixed to the prevertebral fascia.

Apart from these theories and observations very little investigation has been carried out as to the precise factors causing the opening and closing of the sphincter during swallowing, and how their coordination with the pharyngeal peristaltic wave is carried out. In addition the part the cricoid plays in the opening of the sphincter is ill-understood.

In the present investigation an attempt has been made to clarify these problems by a series of experiments in the dog. After determining the changes that occur in the sphincter during a swallow reflexly initiated by stimulation of the pharynx, the effect of division of various nerves in the neck on these changes has been studied. In addition other physical factors which might effect the sphincter during swallowing were investigated.

Cineradiographs of swallowing in man have been examined in an attempt to determine if cricoid movement plays an active part in the opening of the sphincter.

Animal Experiments

The dog was used as it is an animal which possesses a well-developed cricopharyngeal sphincter (Fig. 1). In addition the anatomy of the nerves in the dog's neck is stated to be similar to that in man except that the vagus carries with it the sympathetic chain throughout most of its cervical course and is called the "vagosympathetic trunk", the two components, however, being quite separate. The branches of the vagus resemble those in man except for a few minor differences, viz. the pharyngeal branch occasionally gives off the median laryngeal nerve which joins the external division of the superior laryngeal nerve supplying the cricothyroid muscle. The recurrent laryngeal has a separate pararecurrent branch the latter nerve in man remaining within the recurrent itself.

It has been shown by Lund & Ardran (1964) that the other difference in the dog is that the cricopharyngeal sphincter is supplied by a separate nerve which is a division of the pharyngeal branch of the vagus arising at the level of, or just above the jugular foramen. Stimulation of this nerve produces contraction of the corresponding cricopharyngeus muscle and experimentally does not appear to supply any other structure.

In order to observe the changes in the sphincter during swallowing and to ensure that a pressure recording device would not be effected by contractions of adjacent muscles, a preparation termed "The Isolated Sphincter" was used (Figs. 2 and 3). This was produced by removing the entire larynx except for the cricoid which was left continuous below with the trachea.

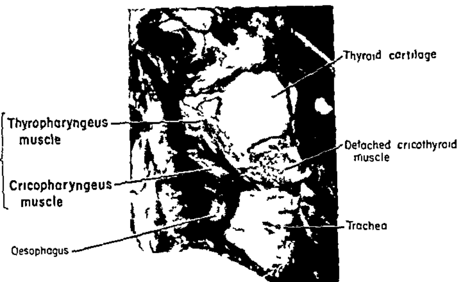


Fig 1 Dissection of the inferior constrictor of a dog

but isolated above The cricopharyngeus muscles were not interfered with and remained attached to the cricoid being continuous with the thyropharyngeus muscles superiorly These in turn were left *in situ* connected to the upper pharynx The dissection was carried out from the deep aspect



Fig 2 "The totally isolated sphincter" Viewed from above

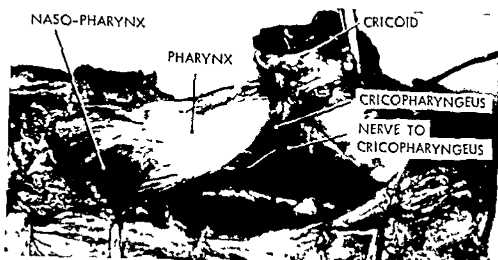


Fig. 3. "The totally isolated sphincter" viewed from the side.

of the pharynx so as to minimise any risk of injury to nerves. Finally, the oesophagus was completely transected 1/2 in. below the lower border of the cricopharyngeus muscles.

In order to record changes in the tone of the sphincter a pressure sensitive device previously described by Lund & Ardran (1964), was inserted into it. This consisted of a perspex rod surrounded by a thin latex tube filled with water under slight tension (Figs. 4, 5 and 6). The instrument was connected to a Schillingford-Muller (Cambridge) pressure transducer and a direct writing recorder. The instrument was found to remain securely in the sphincter while it contracted and relaxed, these changes being recorded as positive and negative waves above the base line respectively.

When nerves required stimulating, rectangular current pulses of 0.3-2.0 m amps. were used, with a duration of 4 m. sec. and a frequency of 20 c/s. A single platinum cathode was used with an anode placed under the dog's back.

Dogs were anaesthetised with intravenous sodium pentobarbitone (Nem

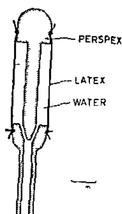


Fig. 4.



Fig 5

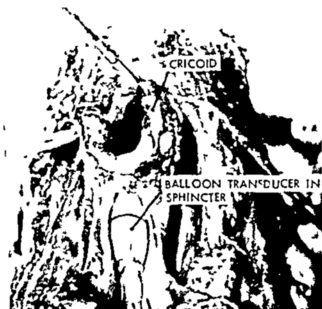


Fig 6

but il Abbotts Laboratories Ltd) the depth of anaesthesia being kept at a level where swallowing could be reflexly initiated by touching the posterior pharyngeal wall

Investigations of the Sphincter Changes During Reflex Swallowing and the Effect of Various Nerve Sections

Normal sphincter changes during reflex swallowing

Before initiating a swallow the cricoid was lifted forwards so that the sphincter lumen could be clearly seen This produced partial opening of the sphincter with the posterior lip of the cricopharyngeus muscles bulging slightly forwards



Fig. 7

A number of selected frames from an ordinary cine film taken of the sphincter from above show the changes that occur during a swallow (Fig. 7). The sphincter initially opens more widely than the resting state (2). This is followed rapidly by a marked contraction of the cricopharyngeus muscles which can be seen to close the sphincter tightly (4). In this particular record it took 6 frames from the fully open state to the tightly closed, i.e. approximately 0.4 sec. The sphincter then relaxes to return to its initial resting state (5).

A pressure recording from the sphincter during two successive reflex swallows confirms the above changes (Fig. 8).

Each tracing is of the same pattern. Initially there is a small positive wave which is due to mechanical displacement of the sphincter by the stimulating



Fig 8 Normal swallow

instrument pulling on the posterior pharyngeal wall from above This is followed by a well marked negative wave corresponding to relaxation of the cricopharyngeus muscles The tracing then rises to a second positive wave of greater amplitude than the first this denoting the stage of marked contraction of the sphincter The tracing then falls to the base line showing that the sphincter relaxes to the initial resting state

Conclusion In a lightly anaesthetised dog a swallow can be produced reflexly by touching the posterior wall of the oropharynx The stimulus is applied at a point well away from the region of the sphincter the changes in which are not therefore produced by a direct effect The sphincter as observed in the isolated preparation passes through four stages, i e resting state widely open sphincter closed sphincter resting state

The fact that the sphincter is seen to open more widely is due to the cricopharyngeus muscles relaxing (as measured by the recording instrument) In this relaxed state the posterior part of the sphincter sags backwards under the influence of gravity and the lumen widens There is of course, space enough for this to occur as the cricoid is held forwards so that the sphincter can be visualised

In addition the pharynx is seen to shorten vigorously during the swallow with marked elevation of the cricoid The latter manoeuvre occurs even though the strap muscles are absent and must therefore, be brought about by the contraction of the pharyngeal muscles The latter raises the sphincter and upper oesophagus together with the attached cricoid

The Effect of Nerve Sections on the Normal Sphincter Changes During Swallowing

In 15 dogs the following nerves were isolated in turn on both sides of the neck viz the nerve to the cricopharyngeus muscle the nerves to the musculature of the middle region of the pharynx and upper part of the inferior constrictor (divisions of the pharyngeal branch of the vagus) the superior laryngeal nerve (and its external and internal branches) and the recurrent laryngeal nerve Each nerve was divided unilaterally and bilaterally After each division a reflex swallow was initiated The sphincter changes during the swallow were observed directly in each case and also measured by the recording instrument

(1) *The nerve to the cricopharyngeus muscle*

There did not appear to be any marked alteration in the normal sphincter changes during swallowing as viewed directly following division of one nerve

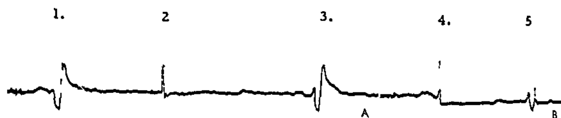


Fig. 9. (A) Divided right N. to cricopharyngeus. (B) Divided left N. to cricopharyngeus.

However, when both nerves were divided the *sphincter was observed to relax* and contract extremely weakly. The pharynx above the sphincter contracted *strongly but only down to the upper border of the cricopharyngeus muscles*, i.e. to the level where the normally innervated pharynx met the weakly functioning sphincter.

A recording from the sphincter (Fig. 9) following unilateral and bilateral division of the nerves to the cricopharyngeus muscles confirms the above *findings* viz.

1. Shows the normal sphincter pattern during a swallow.

2. This positive peak is due to a momentary contraction of the right cricopharyngeus muscle at the instant the right nerve was divided.

3. This shows that the sphincter changes are unaltered by unilateral division *of the nerve to the cricopharyngeus muscle*.

4. This positive peak is due to the left nerve being divided, contraction of the left cricopharyngeus muscle occurring at this instant. Following this peak the baseline has fallen slightly denoting a small reduction in the tone of the sphincter.

5. *Shows the sphincter changes following bilateral division of the nerves to* the cricopharyngeus muscles. There is the usual initial positive wave (mechanical disturbance of the sphincter) followed by very small negative and positive waves thus confirming the presence of the weak relaxation and contraction phases.

Conclusion. *Division of one nerve to the cricopharyngeal* sphincter does not appear to have any effect on either the resting tone of the sphincter or its fundamental changes during swallowing. Division of both nerves, however, produces marked changes. The tone of the sphincter is reduced slightly and during swallowing the sphincter relaxes and contracts in a weak and inefficient manner.

(2) *The nerves to the middle part of the pharynx and upper part of the inferior constrictor (thyropharyngeus muscle)*

Unilateral and bilateral division of these nerves (with the nerves to the cricopharyngeus muscles intact) did not appear to alter the normal sphincter changes during the swallow. Pressure recordings confirmed this observation, the tracings showing the usual well marked relaxation and contraction phases. The pharynx was seen *to shorten during* the swallow (although not as strongly as normal) in spite of bilateral division of these nerves. Total denervation of the middle and lower pharynx, i.e. as in the above experiment but also *with division of the*

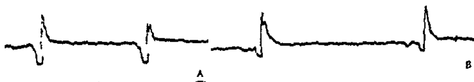


Fig 10 (A) Normal swallow (B) Sphincter detached from prevertebral fascia

nerves to the cricopharyngeus muscles produced the expected weakly functioning sphincter

Conclusion Unilateral and bilateral denervation of the pharyngeal constrictors above the cricopharyngeus muscles does not alter the fundamental swallowing changes in the sphincter, as long as the nerves to the cricopharyngeus muscles are intact Although division of the former nerves effects the constrictors in this region, the pharynx still shortens during a swallow suggesting that total denervation has not been accomplished

(3) The superior laryngeal nerve (and its external and internal branches) and the recurrent laryngeal nerve

Division of these particular nerves both unilaterally and bilaterally produced no alteration of the sphincter changes during swallowing

Neither the recurrent laryngeal nerve nor the superior laryngeal nerve plays any part in the function of the sphincter during swallowing

The Effect of other Factors on the Sphincter Changes during Swallowing

(1) The effect of detaching the sphincter from the prevertebral fascia

The sphincter with approximately 2 in of the pharynx above and *oesophagus* below were dissected free from its connective tissue attachments to the prevertebral fascia

Following this procedure the normal sphincter changes were observed to occur during swallowing Pressure recordings confirm this except that the relaxation phase is slightly less marked as compared with the normal (*Fig 10*)

Conclusion Detachment of the sphincter from the *prevertebral fascia* does not appear to make any marked difference to the fundamental sphincter changes during swallowing

(2) The effect of displacement of the cricoid forwards after detachment of the sphincter from the prevertebral fascia

The sphincter was dissected free *from the* prevertebral fascia The effect on the lumen of the sphincter of moving the *cricoid* forwards was then observed

If the cricopharyngeus muscles were tightly contracted … forward … crico … ing of … the sphincter was *detached* from the prevertebral fascia

Conclusion If forward movement of the cricoid plays any *part in the* open

ing of the sphincter, then the state of relaxation (or contraction) of the cricopharyngeus muscles is of more importance than the attachment of the sphincter to the prevertebral fascia.

(3) *The effect of direct electrical stimulation of the upper pharyngeal musculature on swallowing*

In an anaesthetised dog which could be made to swallow reflexly the stimulating cathode was placed directly on various parts of the superior and middle constrictors and the nerves supplying them.

These particular muscles contracted strongly and produced shortening of the pharynx but no response at any time was observed in the sphincter.

Conclusion. Direct pharyngeal contraction does not initiate a swallow or the physiological changes in the sphincter associated with it. Sensory stimulation of the pharynx is required to produce the reflex.

(4) *The effect of detaching the pharynx from the sphincter, the nerves to the cricopharyngeus muscles being intact*

The pharynx was completely severed in its whole circumference from the sphincter at a level just above the upper border of the cricopharyngeus muscles, the nerves to the latter being left intact.

During swallowing it was observed that the detached proximal pharynx underwent a strong contraction but the sphincter did not alter in any way.

Conclusion. If continuity is broken between the pharynx and the sphincter normal sphincter changes during swallowing do not occur even though the nerves to the cricopharyngeus muscles are intact. This effect may be due to interruption of either the muscle layer itself or nerve fibres present in the pharyngeal wall.

(5) *Effect on sphincter of rotating the cartilages of Santorini forwards*

The larynx of a dog was opened via a laryngofissure approach. After retracting each half of the thyroid cartilage laterally the two cartilages of Santorini were identified. Each cartilage in turn and then both simultaneously were pulled forwards towards the laryngeal prominence.

During these procedures the sphincter was watched directly via a laryngoscope and pressure recordings were taken from the sphincter and upper oesophageal lumen. The sphincter did not open or relax at any time during movement of either one or both cartilages of Santorini.

Similar rotation forwards of the arytenoids had no effect on the sphincter.

Conclusion. There is no evidence from this experiment to support the theory that forward movement of the cartilages of Santorini open the top of the oesophagus in the dog during swallowing.

DISCUSSION

From the results of the preceding experiments it has been determined that during a reflexly induced swallow in the dog the cricopharyngeus

muscles first relax, then contract and finally return to the initial resting state. The relaxation phase is independent of any attachment of the sphincter posteriorly to the prevertebral fascia. It must also occur irrespective of forward movement of the cricoid since it happens in the isolated preparation in which there are no muscles left attached to the cricoid that could produce this change. In order that these changes should occur in the dog, at least one of the nerves to the cricopharyngeus muscles must be intact and continuity is essential between the pharynx above and the sphincter below. The sphincter changes were initiated reflexly and required an intact sensory nervous system. The swallowing complex could not be promoted by direct stimulation of the motor system, i.e. the nerves to the constrictor muscles or the muscles themselves.

There does not appear to be experimental evidence in the dog that any other nerve plays a part in the sphincter changes. In particular bilateral division of the recurrent laryngeal nerves did not alter the sphincter behaviour in any way.

In addition there is no experimental support for Negus' theory that forward movement of the cartilages of Santorini play a part in the opening of the sphincter in the dog during swallowing.

The closed state of a resting sphincter is probably maintained by the normal tone existent in striated muscle and to a lesser extent by the presence of an extrinsic nerve supply. In the dog it has been shown that division of the nerves to the cricopharyngeus muscles lowers the resting tone but does not abolish it. The sphincter can alter from this closed state by means of active contraction or relaxation of the cricopharyngeus muscles, these two changes occurring during a normal swallow. However, in order to *open the* sphincter, i.e. to produce a visible lumen, the cricoid has to move forwards since its posterior aspect is normally resting against the soft tissue covering of the vertebral column. To enable this to happen, the cricopharyngeus muscles must be in a state of relaxation and this appears *to be the most* important factor rather than the attachment of the sphincter to the prevertebral fascia.

From the examination of many normal cineradiographic films of swallowing in man the cricoid has never been seen to *move forwards* and open the sphincter before the bolus has arrived. In a few instances this has appeared to be the case but *on closer examination* it was seen that barium was preceded by air, the latter acting as *the bolus*. It was seen that as long as the cricopharyngeus muscles have relaxed then a bolus will pass through the sphincter if it has *sufficient* propulsive force. This is borne out by a cine record of a subject swallowing in the completely inverted position. A first swallow was performed and the barium passed upwards through the sphincter into the oesophagus. The bolus was prevented from flowing downwards (cephalically) into the pharynx by the tonically closed sphincter. A second swallow *followed* and as the bolus entered the pharynx, the sphincter relaxed, the first bolus immediately passed downwards (cephali-

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Conclusion There is no evidence from this experiment to support the theory that forward movement of the cartilages of Santorini open the top of the oesophagus in the dog during swallowing

DISCUSSION

From the results of the preceding experiments it has been determined that during a reflexly induced swallow in the dog the cricopharyngeus

muscles first relax, then contract and finally return to the initial resting state. The relaxation phase is independent of any attachment of the sphincter posteriorly to the prevertebral fascia. It must also occur irrespective of forward movement of the cricoid since it happens in the isolated preparation in which there are no muscles left attached to the cricoid that could produce this change. In order that these changes should occur in the dog at least one of the nerves to the cricopharyngeus muscles must be intact and continuity is essential between the pharynx above and the sphincter below. The sphincter changes were initiated reflexly and required an intact sensory nervous system. The swallowing complex could not be promoted by direct stimulation of the motor system, i.e. the nerves to the constrictor muscles or the muscles themselves.

There does not appear to be experimental evidence in the dog that any other nerve plays a part in the sphincter changes. In particular bilateral division of the recurrent laryngeal nerves did not alter the sphincter behaviour in any way.

In addition there is no experimental support for Negus' theory that forward movement of the cartilages of Santorini play a part in the opening of the sphincter in the dog during swallowing.

The closed state of a resting sphincter is probably maintained by the normal tone existent in striated muscle and to a lesser extent by the presence of an extrinsic nerve supply. In the dog it has been shown that division of the nerves to the cricopharyngeus muscles lowers the resting tone but does not abolish it. The sphincter can alter from this closed state by means of active contraction or relaxation of the cricopharyngeus muscles, these two changes occurring during a normal swallow. However, in order to *open* the sphincter, i.e. to produce a visible lumen, the cricoid has to move forwards since its posterior aspect is normally resting against the soft tissue covering of the vertebral column. To enable this to happen the cricopharyngeus muscles must be in a state of relaxation and this appears to be the most important factor rather than the attachment of the sphincter to the prevertebral fascia.

From the examination of many normal cineradiographic films of swallowing in man the cricoid has never been seen to move forwards and open the sphincter before the bolus has arrived. In a few instances this has appeared to be the case but on closer examination it was seen that barium was preceded by air, the latter acting as the bolus. It was seen that as long as the cricopharyngeus muscles have relaxed then a bolus will pass through the sphincter if it has sufficient propulsive force. This is borne out by a cine record of a subject swallowing in the completely inverted position. A first swallow was performed and the barium passed upwards through the sphincter into the oesophagus. The bolus was prevented from flowing downwards (cephalically) into the pharynx by the tonically closed sphincter. A second swallow followed and as the bolus entered the pharynx the sphincter relaxed, the first bolus immediately passed downwards (cephali-

cally) through the now relaxed sphincter into the pharynx under the action of gravity and mixed with the second bolus

The above observations and experiments appear to support the following theory as to the preliminary action of the sphincter during swallowing. The sphincter relaxes (not opens) ahead of the bolus. The bolus be it food, barium or air, on reaching the relaxed sphincter is able to pass through under the action of gravity and thrust from the tongue above. The cricoid moves forwards to provide sufficient space to allow the bolus to pass between its posterior surface and the soft tissue covering the vertebral column. The bigger the bolus, the more room is required and the further forward the cricoid moves.

CONCLUSION

In order to fit the experimental findings in the dog into an explanation of how the sphincter behaves during swallowing, it is suggested that its changes are probably due to a reflex arc, stimulated by the peristaltic wave when it reaches a level just above the sphincter (it is likely that this "sphincter reflex" is merely part of a series of coordinated reflexes which give rise to the peristaltic wave itself). It is also suggested that the nerves to the cricopharyngeus muscles constitute the efferent pathway of this reflex arc. The fibres passing in these nerves are either excitatory or inhibitory, producing contraction or relaxation of the sphincter respectively. The latter change is probably due to a reduction of the nerve impulses which normally pass continuously to the sphincter maintaining its resting tone. The arrangement of the afferent pathway is uncertain but it may be formed by nerve fibres in the pharyngeal wall derived from the pharyngeal branch of the vagus nerve.

When a swallow is produced by stimulation of the upper pharynx, an initial wave of relaxation passes downwards. When it reaches a point just above the sphincter, the reflex arc is stimulated and the sphincter relaxes. This is followed by a contraction wave which also passes down the pharynx but in this case stimulates the reflex to produce contraction of the sphincter. Thus the sphincter initially relaxes and then contracts, both changes being coordinated with the peristaltic wave.

When the pharynx is divided above the sphincter, the peristaltic wave is unable to pass downwards in the normal way. As a result the afferent pathway is not stimulated and the normal sphincter changes do not occur even though the nerves to the cricopharyngeus muscles are intact. Similarly, the sphincter again fails to function normally if the nerves to the cricopharyngeus muscles are divided but the pharynx is continuous with the sphincter. In this case it is the efferent pathway which has been destroyed.

On this basis, if the downward passage of the peristaltic wave is stopped by denervating the constrictors above the sphincter, then stimulation of the reflex arc would again be prevented with failure of the normal sphincter

changes to occur. Experimentally, however, this was not confirmed. The sphincter functioned normally and the pharynx still shortened, though not as vigorously as in a normal swallow. It would seem that total denervation of this part of the pharynx had not been accomplished and the peristaltic wave although weak, was still able to pass downwards without stopping at this particular level.

Although the above findings suggest that relaxation of the cricopharyngeal sphincter occurs immediately ahead of the pharyngeal peristaltic wave, there is also cineradiographic evidence that relaxation can occur before the peristaltic wave even begins. This relaxation is probably central in origin, arising from the swallowing centre in the medulla.

The findings in the dog, however, can be criticised on the grounds that the experiments were performed in the isolated preparation. This preparation is certainly an unphysiological one as the larynx and hence the origin of attachment of the middle part of the pharyngeal musculature, has been removed. However, the sphincter can still contract and relax as in a normal dog since the cricoid is left in situ in the preparation with the two cricopharyngeus muscles undisturbed. In addition, although the larynx has been removed the deglutition reflex is still present and can be initiated easily. It is felt, therefore, that the results of swallowing experiments in this investigation are perfectly valid. The advantage of the preparation is obvious since the sphincter can be seen directly and the position of the recording instrument checked continuously throughout the various procedures.

ACKNOWLEDGMENTS

I would like to express my gratitude to Dr. G. M. Ardran of the Nuffield Institute for Medical Research, Oxford, for all his constant help and advice throughout this investigation. My thanks are also due to Dr. G. Dawes, Director of the Nuffield Institute for Medical Research, for providing me with facilities for the experimental work. I would like to thank Mr. R. G. Macbeth and Mr. G. H. Livingstone of the Department of Otolaryngology, The Radcliffe Infirmary, Oxford, for all their help and for allowing me to review their patients. I am indebted to the Nuffield Committee for the grant which has enabled this investigation to be carried out. My thanks are due to Dr. G. M. Ardran and Dr. F. H. Kemp of the Radiology Department, The Radcliffe Infirmary, Oxford, for allowing me complete access to their cineradiographic films and for the opportunity of studying them. I am also indebted to Miss E. Emrys Roberts and Mr. M. S. Tuckey for all their technical assistance.

ZUSAMMENFASSUNG

Experimentelle Untersuchungen an Hunden und kinematographische Röntgenaufnahmen bei Menschen (25 Einrahmen pro sec.) wurden ausgeführt, um Veränderungsprozesse zu studieren, die sich beim Schluckakt im Bereiche des cricopharyngealen Schliessmuskels ereignen. Im gewöhnlichen Ruhezustand bietet der

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On this basis, if the downward passage of the peristaltic wave is stopped by denervating the constrictors above the sphincter then stimulation of the reflex arc would again be prevented with failure of the normal sphincter

EFFECTS OF BILATERAL CALORIC HABITUATION ON VESTIBULAR NYSTAGMUS IN THE CAT

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Transfer of bilateral caloric nystagmus habituation to unilateral calorization was investigated in a group of 60 cats. Habituation to bilateral caloric irrigations markedly reduced responses to both less intense and more intense unilateral stimulation.

Subsequent testing provided information concerning the effects of caloric habituation on: (1) directional specificity of response, (2) retention of the response decline, and (3) optokinetic nystagmus. Statistical analyses also indicated a sex difference in response magnitude.

It has been suggested that the decline (habituation) of the nystagmic response to repeated vestibular stimulation is a form of learning in that it possesses the necessary features of a learned behavior—acquisition, retention, and transfer (Halstead, 1935). Acquisition of habituation is evidenced through the progressive reduction of the response with repeated stimulation, while retention has been reported for periods as long as several weeks (Halstead, 1935; Henriksson, Kohut & Fernandez, 1961).

Transfer of unilateral caloric nystagmus habituation was shown to occur when a previously non-stimulated ear was irrigated with a stimulus provoking a response in the same direction as that elicited during habituation of the contralateral ear; responses elicited in the unhabituated direction were reported to be vigorous (Collins, 1964 *a*; Henriksson, Kohut & Fernandez, 1961). This apparent directional specificity of transfer has also been shown for (bilateral) habituation to mild angular acceleration (Crampton, 1962). However, studies have generally reported a failure to obtain transfer of habituation from one means of stimulation (e.g., rotatory) to another (e.g., caloric) in spite of the fact that both types of stimuli evoked responses in the same direction (Collins, 1964 *a*, *b*; Hood & Pfaltz, 1954; Maxwell, Burke & Reston, 1922). The single study reporting a stimulus transfer effect (from caloric to rotatory stimulation) used extensive irrigations of ice water to

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genannte Schliessmuskel einen starken Widerstand, welcher den Rückfluss des Inhaltes des Schlundes nach oben verhindert. Dieser Ruhezustand ändert sich beim Hunde während des Schluckaktes, indem sich der cricopharyngeale Schliessmuskel zuerst entspannt und nachher wieder zusammenzieht. Diese Abweichungen im Bereiche des Schliessmuskeltonus und dessen Störungen konnte man nachweisen durch Anwendung einer genauen Druckmessapparatur, welche an den genannten Sphinkter eingeschaltet wurde. Der Mechanismus dieses Prozesses hängt ab in erster Linie von der Unversehrtheit wenigstens eines Nerven, welcher den Ringknorpelschliessmuskel versorgt, sowie auch vom fortgesetzten Zusammenhang der pharyngealen und hypopharyngealen Muskulatur miteinander. Kinematographische Röntgenaufnahmen bei Menschen zeigen, dass der Bolus, der den entspannten Schliessmuskel erreicht, weiter leicht durchgeht dank der Wirkung der Schwerkraft und dem stossenden Antrieb der Zungenmuskulatur von oben. Es ist nicht beweisgebend, dass Vorwärtsbewegungen des Ringknorpels den cricopharyngealen Schliessmuskel früher öffnen als Bolus es getan hat. Andeutungen wären zu prüfen, wie sich diese Veränderungsprozesse in der cricopharyngealen Schliessmuskulatur in bezug auf die pharyngeale Peristaltik verhalten, insbesondere während des Schluckaktes.

REFERENCES

Ardran, G. M., and Kemp, F. H., 1955: A radiographic study of movements of the tongue in swallowing. *The Dental Practitioner, 5*, 252.

— 1961: The radiography of the lower lateral food channels. *J. Laryng., 75*, 358.

Barclay, A. E., 1936: *The Digestive Tract. A Radiological Study of its Anatomy, Physiology and Pathology*. London: Cambridge University Press, pp. 132–142.

Dohlman, G., and Mattsson, O., 1959: The role of the cricopharyngeus muscle in cases of hypopharyngeal diverticula. *Amer. J. Roentgenol., 81*, 561.

Fyke, F. E., and Code, C. F., 1955: Resting and deglutition pressures in the pharyngo-oesophageal region. *Gastroenterology, 29*, 24.

Lerche, W., 1950: *The Esophagus and Pharynx in Action*. Charles C. Thomas, pp. 169–171.

Lund, W. S., and Ardran, G. M., 1964: The motor nerve supply of the cricopharyngeal sphincter. *Ann. Otol.* (in press).

Negus, V. E., 1949: *The Comparative Anatomy and Physiology of the Larynx*, pp. 91–9[illegible].

Schreiber, J., 1904: *Über den Schluckmechanismus*. August Hirschwald, Berlin.

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TABLE 1 *Schedule of test stimuli for each group*

Group	Test			
	Pretest (1 trial)	Habituation (15 trials)	Post 1 (1 trial)	Post 2 (1 trial)
AC	Unilateral 26°C–30 sec	Unilateral 26°C–30 sec	Unilateral 26°C–30 sec	Unilateral IW–15 sec
AI	Unilateral 26°C–30 sec	Bilateral 25 sec	Unilateral 26°C–30 sec	Unilateral IW–15 sec
AII	Unilateral 26°C–30 sec	Bilateral 30 sec	Unilateral 26°C–30 sec	Unilateral IW–15 sec
BC	Unilateral IW 15 sec	Unilateral IW–15 sec	Unilateral IW–15 sec	Unilateral 26°C–30 sec
BI	Unilateral IW 15 sec	Bilateral 15 sec	Unilateral IW–15 sec	Unilateral 26°C–30 sec
BII	Unilateral IW–15 sec	Bilateral 20 sec	Unilateral IW–15 sec	Unilateral 26°C–30 sec

Note—All unilateral trials were administered to the right ear. Bilateral trials consisted of simultaneous irrigations of 26°C (right ear) and 50°C (left ear). IW indicates ice water (4°C)

the drum. Eye-movements induced by a constant rotatory velocity (4 rpm) of the drum were recorded and scored for each animal to obtain a calibration value relating degrees of eye-movement (assuming perfect following) to millimeters of pen deflection.

Procedure

The 6 habituation procedures are shown in Table 1. Each procedure comprised 18 trials, a pretest, 15 habituation trials, a post-1 test (identical to the pretest), and a post 2 test of a different intensity. In each case, a nystagmus to the left was induced. The pre-, post-1 and post 2 tests were unilateral irrigations applied in all cases to the right ear. All trials were administered on the same day, at 20 min intervals. The irrigation and recording periods were always in total darkness, but animals were in full-room illumination for a period not less than 5 min before a trial began.

Four groups (AI, AII, BI, BII) were habituated to a series of 15 simultaneous bilateral irrigations of 50°C in the left ear and 26°C in the right ear. In order to obtain some information concerning the effects of time-of-irrigation on response magnitude, the duration of the bilateral habituating stimulus was different for each of these groups (BI 15 sec, BII 20 sec, AI 25 sec, AII 30 sec).

The bilateral habituation stimuli for groups AI and AII were used to produce responses of greater magnitude than the unilateral irrigation (26°C for 30 sec) administered as a pre- and post-1 test. Groups BI and BII re-

abolish completely the nystagmic response (from each ear separately) *before* the rotation trials were administered (Dunlap 1925).

The present study was designed to examine some aspects of transfer of nystagmus habituation. Bilateral caloric irrigations (warm water *in one ear*, cool in the other) were employed to provide simultaneous deflection of the cupulae. Transfer of the response decline was checked by administering unilateral irrigations following different series of *bilateral calorizations*. *Subsequent testing* permitted an evaluation of various other aspects of vestibular habituation.

METHOD

Sixty cats, unused in previous experiments, served as subjects. The animals, *restrained by the method of Henriksson, Fernandez & Kohut (1961)* and with their heads elevated to an optimal position, were divided into 6 equal groups. Each group underwent caloric habituation under different *stimulus conditions*.

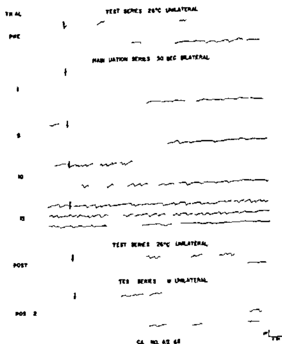
Stimulation

Three water baths were used. One contained ice water at a temperature of 4°C (±0.5°C), while the remaining 2 were equipped with Bronwill constant temperature circulators which maintained water temperature at 26°C *and 50°C (±0.01°C) respectively (approximately 12°C above and below* the cats' body temperature). Rubber tubing with attached irrigation nozzles provided the means for introducing the stimuli to the ears of the animals. *The rate of flow (and therefore the total volume of water)* was high (approximately 12 cc/sec) to permit a ready monitoring by touch of the return flow from the ear and assure delivery of the stimulus in total *darkness*.

Recording and scoring

Recordings of nystagmus were obtained with an Offner Type T Electroencephalograph (time constant 3 sec), located in an adjoining room. The corneoretinal potentials were detected by needle electrodes inserted at the outer canthi of the cats' eyes.

Records were scored from the point of stimulus termination for number of beats, duration of nystagmus and slow phase displacement of the eyes. The number of nystagmic eye movements (beats) were simply counted for each trial. Response duration was measured from the termination of the irrigation to the last beat of the primary nystagmus. The amount of slow phase eye movement was obtained in millimeters by measuring the vertical displacement of each nystagmic beat from the peak to the base line. These values were summed for each trial and transformed into degrees by means of calibration constants obtained with an optokinetic stimulator. The latter consisted of a drum 2 1/2 ft high and 4 ft in diameter driven by a DC motor. Alternate black and white vertical stripes covered the interior of



Fi 1 Recorded nystagmus from a cat in group AII Upwar l deflection of the pen lenotes a movement of the eyes to tl e right downward deflection to the left Vertical bars tl rcugl the tracings mark the termination of tl e stimulus Tl e bilateral l al tu ting stimulus was more inte se tl an tl at of tl e unilateral pre an l post 1 tests

phase graph but no distinct differentiation of the groups in the duration data

All groups exhibited the greatest amount of decline in the first 5 trials of the habituation series (Fig 2) Other studies have noted this charac teristic of the response curves for habituation to unilateral caloric stimula tion and to angular acceleration (Collins 1964 *a b* Griffith 1920)

Pretests and post 1 tests The stimulus for the pre and post 1 test for all A groups was a 26°C unilateral irrigation for 30 sec In order to determine the influence of the bilateral habituation trials on responses to the less intense unilateral stimulus analyses of co variance were conducted on the pre and post 1 test scores for the slow phase number of beats and dura tion measures No significant differences were found among the 3 A groups on any measure That is habituation to bilateral caloric stimulation trans ferred to a unilateral irrigation of lesser intensity

Post 2 tests The post 2 stimulus for the A groups was a 1 sec unilateral ice water (IW) irrigation For all groups the response to the IW trial was greater than that to the post 1 (26°C) stimulus (see Fig 2) The increased amount of response to the IW trial was notably marked for the AC (control) group

ceived bilateral habituation stimuli which were selected to produce less vigorous responses than a pre- and post-1 test of ice water (4°C for 15 sec)

Two control groups (AC and BC) were habituated to unilateral irrigations identical to the pre- and post-1 test stimulus of their respective groups (AC. 26°C for 30 sec; BC: 4°C for 15 sec). These control animals provided a measure of the level of response after unilateral habituation Therefore, comparison of the post-1 test responses of one set of experimental (AI and AII) and control (AC) groups provided the basis for examining the question of transfer of habituation from a bilateral caloric series to a less intense unilateral stimulus Likewise, comparisons of post-1 test responses of BI and BII with those of BC indicated the extent of transfer from a bilateral habituation series to a more intense unilateral stimulus

The post-2 test stimulus for the A groups was the same as the pre- and post-1 test stimulus of the B groups The B groups received post-2 tests identical to the pre- and post-1 tests of the A groups

RESULTS AND DISCUSSION

I. *Effects of Bilateral Caloric Habituation on Responses to Unilateral Stimulation*

A Groups

The experimental groups (AI and AII) received habituation trials of greater intensity than the pretest and post-1 test Figure 1, tracings of nystagmus from an animal in group AII, shows the variation in response magnitude to the bilateral and unilateral stimuli

Habituation series Figure 2 shows the declining mean response-per-trial of the A groups plotted as percentages of the pretest score Analyses of variance were conducted on those data for trials 1 and 15 For the 3 A groups, the habituation series produced a statistically significant reduction in slow-phase displacement and number of beats (.001 level), but not in response duration Previous studies have indicated that duration tends to be the least reliable measure of response decline (Fernandez & Schmidt, 1962, Henriksson, 1956, Ward & Fernandez, 1963)

Significant differences were also found among the groups for slow-phase displacement (.05 level) and number of beats (.01 level) Multiple comparisons were made (.05 level) with the Duncan test (Edwards, 1960) These comparisons showed that the control group yielded fewer beats and less slow-phase output than did either experimental group Although the experimental groups did not differ significantly from each other in slow-phase displacement group AII tended toward greater slow-phase output, and produced a significantly greater number of nystagmic beats than did AI These relations are evident in the curves of Figure 2 in which there are 3 distinct levels of response in the number-of-beats graph, 2 in the slow-

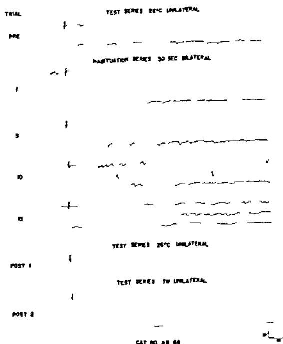


Fig 1 Recorded nystagmus from a cat in group AII Upward deflection of the pen denotes a movement of the eyes to the right downward deflection to the left Vertical bars through the tracings mark the termination of the stimulus The bilateral habituating stimulus was more intense than that of the unilateral pre and post 1 tests

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Post-2 tests The post 2 stimulus for the A groups was a 15 sec unilateral ice water (IW) irrigation For all groups the response to the IW trial was greater than that to the post-1 (26°C) stimulus (see Fig 2) The increased amount of response to the IW trial was notably marked for the AC (control) group

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The post-2 test stimulus for the A groups was the same as the pre- and post-1 test stimulus of the B groups. The B groups received post-2 tests identical to the pre- and post-1 tests of the A groups.

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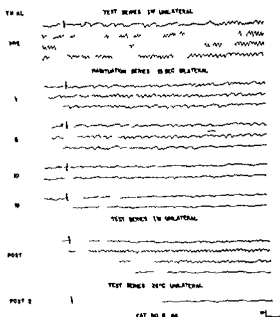


Fig 3 Nystagmus tracings of an animal in group BI Markings are the same as in Figure 1 The bilateral habituating stimulus was less intense than that of the pre- and post 1 tests

B Groups

The experimental groups (BI and BII) received pretests and post 1 tests of greater intensity than the habituation trials Tracings of *nystagmus* depicting this relation appear in Figure 3

Habituation series Reduction of the nystagmic response occurred in each group as a result of the repeated trials of the habituation series In Figure 4 the data are plotted as percentages of the pretest response and statistical analyses were conducted on these scores for trials 1 and 15 Reductions in response significant at the 001 level were found for slow phase displacement and number of beats Duration data which were highly variable, yielded no significant differences between trials 1 and 15 A significant (05 level) trials × groups interaction effect for the slow phase data appeared to be a result of differences in the slopes of the habituation curves (see Fig 4)

Group differences significant at the 01 level were found for all 3 measures of nystagmus and multiple comparisons were made (05 level) with Duncan's test (Edwards 1960) These comparisons showed that the control group produced a significantly greater number of nystagmic beats and more slow phase output than did either experimental group, the experimental groups did not differ from each other in nystagmus production Duration scores were significantly different among all groups, with BC

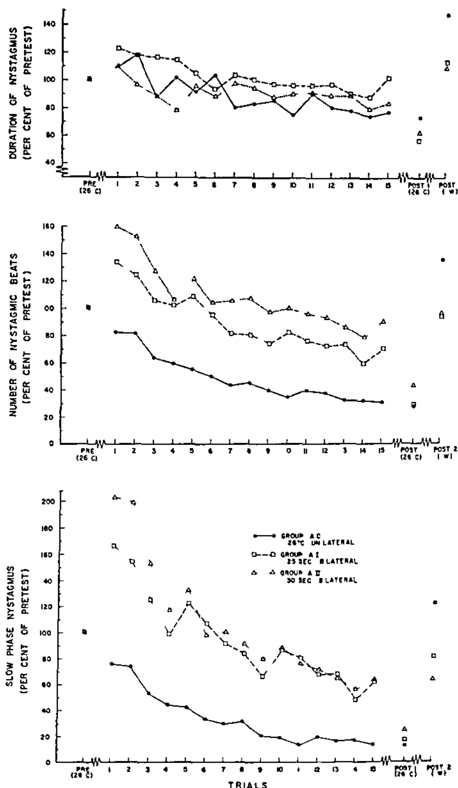


Fig. 2. Mean slow phase eye movement, number of beats, and response duration of the A groups plotted as percentages of the pretest score. Groups AI and AII received bilateral habituating stimuli of greater intensity than the unilateral habituating stimulus applied to AC.

greater than BI or BII and BI greater than BII These differences are evident in the curves of Figure 4 which show 3 levels of duration scores and 2 levels (control and experimental) for the slow phase data and the number of beats

Pretests and post 1 tests The stimulus for these tests (15 sec unilateral IW irrigation) was of greater intensity than the habituation stimuli for the experimental groups (Figs 3 and 4) Analyses of covariance were conducted on the 3 types of scores No significant differences were found among the groups Thus habituation to bilateral caloric stimuli transferred to a more intense unilateral irrigation

Post 2 tests The post 2 test stimulus for the B groups was a 26°C unilateral irrigation for 30 sec This was the weakest of all group B stimuli and it uniformly produced the least response given by these animals on any trial

General Discussion of A and B Groups

A habituation series of bilateral caloric irrigations has a pronounced effect upon the vestibular response to a unilateral irrigation regardless of differences in intensity Statistical analyses showed that nystagmus output to unilateral trials after bilateral habituation was not significantly different from the response level of animals habituated to that same unilateral stimulus This finding indicating a transfer of habituation differs from the studies using rotation as the bilateral habituation stimulus (Collins 1964 I Hood & Pfaltz 1954 Maxwell *et al* 1922) In the latter instances habituation to rotation had no marked reductive effect on subsequent unilateral caloric irrigations The fact that intensity differences existed between the rotatory habituation stimuli and the caloric transfer tests apparently does not account for the minimal amount or absence of transfer reported

In the present study intensity appears to be a negligible factor in bilateral to unilateral transfer of caloric habituation but it may have exterted influence in the unilateral to unilateral situation The latter effect is shown in the vigorous responses of group AC (habituated to 26°C unilateral irrigations) to the post 2 unilateral stimulus of ice water Although probably affected to some extent by the previous habituation trials these IW responses did not appear to be markedly reduced (Fig 2)

Some hypotheses concerning the reported failure of (bilateral) rotational habituation to transfer to (unilateral) caloric stimulation may be offered It is possible that calorization (a gross stimulus compared to angular acceleration) activates neural elements in addition to those related to the lateral semi-circular canal that exact placement of the head is extremely critical when shifting subjects from the optimal caloric to the optimal rotational position or that change in the position of the head from the

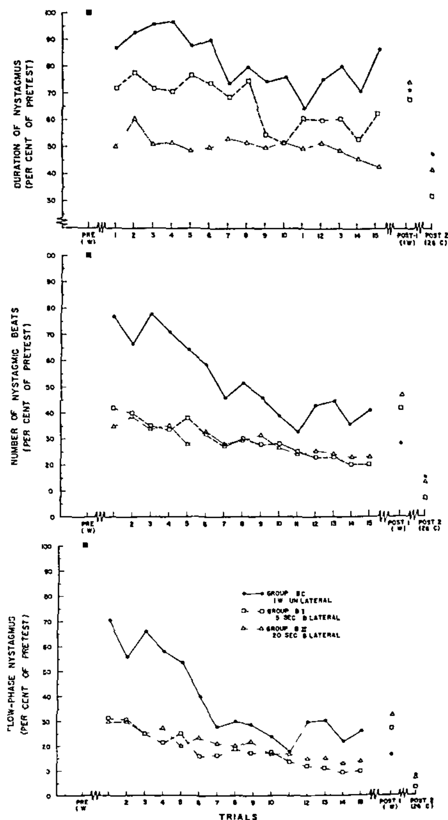


Fig. 4. Mean slow phase eye movement, number of beats, and response duration of the B groups plotted as percentages of the pretest score. Groups BI and BII received bilateral habituating stimuli of less intensity than the unilateral habituating stimulus applied to BC.

greater than BI or BII and BI greater than BII. These differences are evident in the curves of Figure 4 which show 3 levels of duration scores and 2 levels (control and experimental) for the slow phase data and the number of beats.

Pretests and post 1 tests. The stimulus for these tests (15 sec unilateral IW irrigation) was of greater intensity than the habituation stimuli for the experimental groups (Figs. 3 and 4). Analyses of co-variance were conducted on the 3 types of scores. No significant differences were found among the groups. Thus habituation to bilateral caloric stimuli transferred to a more intense unilateral irrigation.

Post 2 tests. The post 2 test stimulus for the B groups was a 26°C unilateral irrigation for 30 sec. This was the weakest of all group B stimuli and it uniformly produced the least response given by these animals on any trial.

General Discussion of A and B Groups

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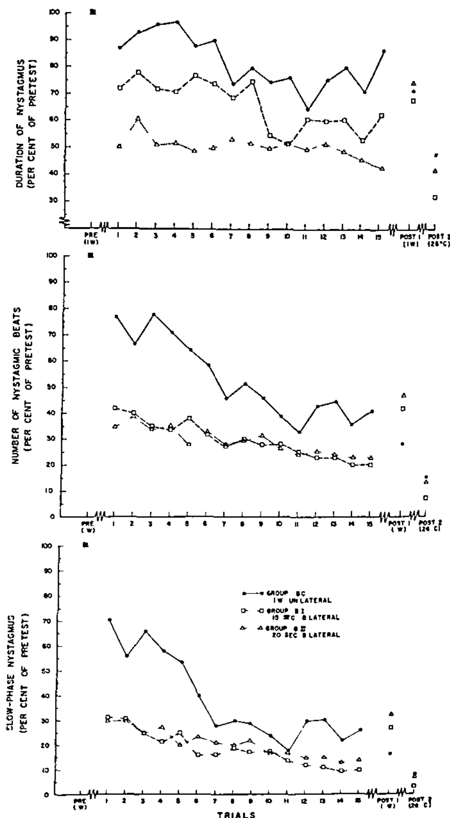


Fig 4 Mean slow-phase eye movement, number of beats and response duration of the B groups plotted as percentages of the pretest score Groups BI and BII received bilateral habituating stimuli of less intensity than the unilateral habituating stimulus applied to BC

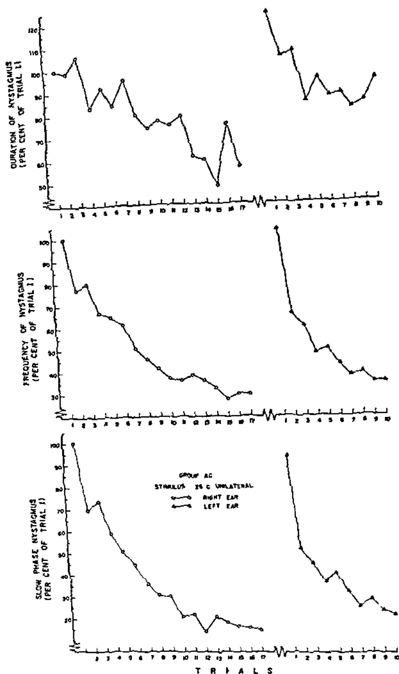


Fig. 5. Trial-by-trial plots of nystagmus scores for group AC, in which habituation was produced for first one direction of nystagmus, and then the other. 17 unilateral irrigations of the right ear with a 26°C stimulus (and an 18th irrigation with IW not plotted) were followed by 10 left-ear stimulations. *Note the* high output on the first left-ear trial and then the rapid drop with succeeding trials.

caloric to the rotatory situation significantly alters the pattern of stimulation from otolithic and proprioceptive receptors One or a combination of these factors might cause sufficient changes in the neural patterning so that the stimulus generalization necessary for transfer of habituation does not occur (cf Guedry 1964)

Duration of an irrigation has been occasionally regarded as a subordinate consideration (especially to temperature effects) in caloric stimulation However pilot studies conducted prior to the present experiments indicated differences in response magnitude of cats to 15 *vs* 25 sec and 20 *vs* 30 sec bilateral stimuli favoring the longer stimulus durations The present experiment allowed comparisons of nystagmus output to less disparate bilateral irrigations *viz* 15 *vs* 20 sec and 25 *vs* 30 sec The former pair differed only in duration and those data were highly variable The 30 sec stimulus produced significantly more nystagmic eye movements than did the 25 sec stimulus and although there was no statistically significant difference in the slow phase data there was approximately 30 per cent more slow phase output in the first few 30 sec trials These data indicate that the duration of irrigation may have some effect on production of nystagmus even with a difference as small as 5 sec It is possible that more pronounced effects of stimulus duration would be evident with lower rates of flow

II *Effects of Bilateral Caloric Habituation on Subsequent Tests*

Directional specificity

Twenty min after receiving the treatments noted above 2 groups AC and BI were given 10 additional habituation trials (with the usual interstimulus intervals) provoking responses in the direction opposite to the original habituation series This was accomplished by stimulating the left ear of cats in the (unilateral habituation) AC group with 26°C irrigations for 30 sec and by interchanging the temperatures (to 26°C left ear and 50°C right ear for 15 sec) for cats in the (bilateral habituation) BI group Figures 5 and 6 show the mean response curves of both groups for the original and the subsequent habituation series for the 3 scored measures The curves for number of beats and slow phase eye movement exhibit a common characteristic that is the marked drop in response within the first 3 4 trials of the subsequent habituation series in contrast with the more gradual decline of the original series Responses to the first trial for each direction of nystagmus are of about the same magnitude for group AC yet the response output drops more rapidly during the early trials in the subsequent tests A similar effect was observed in the data obtained from group BI although here the beginning levels of the 2 habituation series are somewhat different Group BI received an IW pretest irrigation and this intense stimulation probably reduced the response to the first habituation trial In spite of the differences in the initial levels the BI curves for the second set of habituation trials exhibit the same exceptionally rapid early decline as that noted

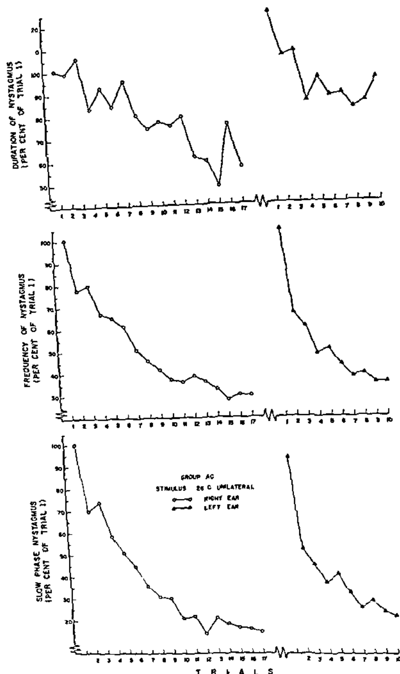


Fig. 9. Trial by trial plots of nystagmus scores for group AC, in which habituation was produced for first one direction of nystagmus, and then the other. 17 unilateral irrigations of the right ear with a 26 C stimulus (and an 18th irrigation with IW not plotted) were followed by 10 left ear stimulations. Note the high output on the first left ear trial and then the rapid drop with succeeding trials.

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for group AC. However, the response for both groups AC and BI do not continue to drop at this rapid rate but rather, level off so that the response to trial 10 of the subsequent series is at the same output level as trial 10 of the original series.

Previous studies (Collins 1964 *a*, Crampton 1962, Henriksson, Kohut & Fernandez 1961) have indicated the apparent independence of direction with regard to vestibular habituation, that is habituation of nystagmus in one direction did not appear to affect the response in the non stimulated direction. These reports were based on a single stimulation in the previously unhabituated direction. In the present study, although the first response in the previously unhabituated direction was quite vigorous, responses to the following 2 or 3 irrigations dropped very rapidly, quite unlike the original decline. Thus it would seem that the first habituation sequence did affect the responses in the non stimulated direction. This apparent bi directional effect of uni directional habituation may be an extension of the transfer characteristic of the learning process postulated earlier (Halstead 1935) in that the animal has learned to control the response to a method of stimulation. The absence of transfer effects on the first trial in the previously non stimulated direction may be partly a result of the novelty of the first irrigation which deters the appearance of learning on that trial, but the effects become more apparent in succeeding trials.

It should be noted that, after the original and subsequent habituation trials, an additional trial identical to those of the original habituation series was performed for each animal. Responses were still at the habituated level. This retention by the cat of habituation in one direction despite subsequent habituation in the other direction confirms the report of Henriksson, Kohut and Fernandez (1961) but differs from findings reported for man (Fluur & Mendel 1962 *a*, *b*).

Retention of habituation

Retention of nystagmus habituation has been reported for periods up to several weeks (Halstead 1935, Henriksson, Kohut & Fernandez 1961). This temporal characteristic of habituation was investigated in group BC (habituated to 15 sec IW irrigations). Four animals from this group were tested one week after and 4 other cats 2 weeks after the original habituation series (see Fig. 7). Retention was tested by 8 IW irrigations in which the ear stimulated was alternated from trial to trial. Half of the animals began with a left ear stimulation, the other half with a right ear stimulation. Figure 8 shows the average responses on the initial series and on the retention series for the 3 scored measures. The small number of animals in each group prevented any reliable analysis of differences between the 1 and 2 week periods and, since data obtained in the retention series were similar for both groups, they were averaged to provide a single response curve. Retention of habituation is apparent in the depicted differences for the habituated and unhabituated directions.

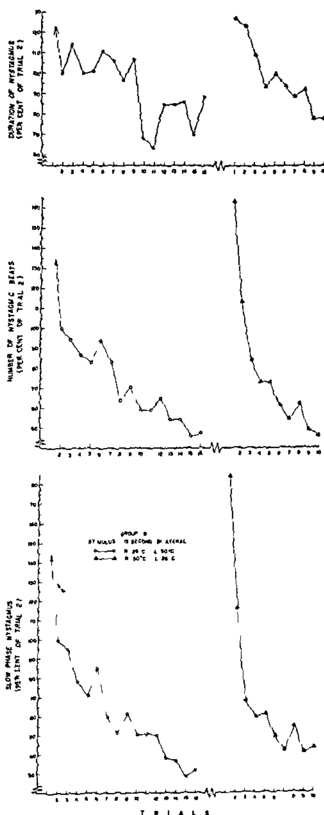


FIG. 6. Trial by trial plots of nystagmus scores for group BI in which habituation was produced for first one direction of nystagmus and then the other. A function similar to that depicted in Figure [?] for group AC is evident for BI although here the "first" trial is probably underestimated since it was preceded by an [?]W irrigation (arrow).

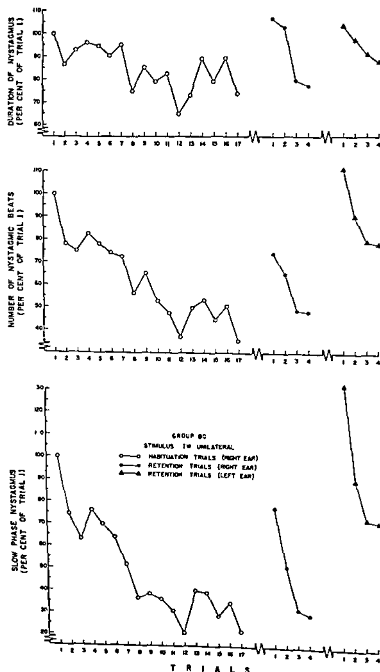


Fig. 8. Retention of habituation in group BC. After initial uni-directional habituation (open circles) 4 cats were tested 1 week later and 4 others 2 weeks later (filled symbols) with nystagmus provoked in both directions. Data for the 1- and 2-week groups were similar and are averaged here. The habituated response shows some recovery in the subsequent testing but declines more rapidly than it did in the original series. The unhabituated direction yields more vigorous responses.

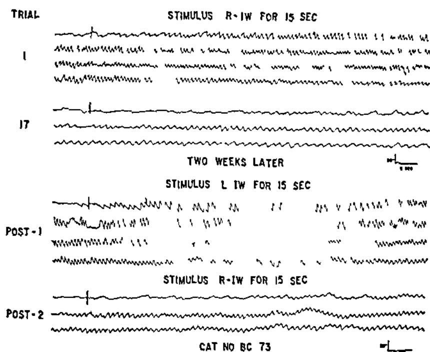


Fig 7 Nystagmograms from a cat which received 17 unilateral IW irrigations When tested 2 weeks later, the response in the habituated direction shows some recovery but is clearly weaker than that of the unhabituated direction Markings are the same as in Figure 1

The course of the response decline obtained in this retention series for the unhabituated direction is very similar to that representing the previously unhabituated responses of groups AC and BI in which the question of directional specificity was examined (compare Figs 5, 6 and 7) Thus responses of group BC to the several trials in the unhabituated direction provide additional evidence for some bi directional effect of uni-directional habituation

Head position

The direction of the nystagmic response to a caloric stimulus can be reversed by a change in head position sufficient to alter the direction of endolymph flow Twenty min after exposure to the habituation sequence previously described, the heads of animals in groups AI and BII were lowered so that the plane of the horizontal canal was changed approximately 110° from the previous test position, and 6 trials were administered The first 3 'head lowered' irrigations for half of the animals in each group were identical to the original habituation stimulus (right ear −26°C, left ear −50°C) while the temperatures were interchanged for the last 3 trials The order of presentation of the 2 temperature combinations was reversed for the remaining animals The lowering of the head changed the direction of nystagmus previously elicited by these stimuli That is, with the head upright, cool water in the right ear and warm water in the left produced

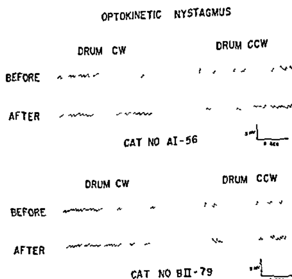


Fig 9 Optokinetic nystagmus obtained from 2 cats Drum speed was 24°/sec

2 bilateral irrigations was alternated from animal-to-animal Responses in the habituated direction remained at a reduced level while responses in the previously non-stimulated direction were vigorous

III *Additional Observations*

Sex differences

Of the 60 animals tested, 38 were females and 22 were males Each male was matched with a female randomly chosen from the same group and *t* tests were conducted on the pretest data Female animals were found to produce a significantly greater (.05 level) amount of response as measured by both slow-phase displacement and number of beats Although this may represent a true sex difference in vestibular functioning, it is quite possibly due only to sex related non-vestibular factors (e g density or mass of bone and other tissue) and may thereby be limited to caloric stimulation There was no statistically significant sex difference in corneo-retinal potential as determined by comparison of the calibration constants

Optokinetic nystagmus

Nystagmographic recordings of eye-movements elicited by both clockwise and counterclockwise rotation of the optokinetic drum were obtained before and after the vestibular trials for 49 animals Calibration constants calculated for each of these exposures were compared statistically to examine possible effects of the habituation series on the optokinetic response. No statistically reliable differences occurred as a result of the intervening vestibular stimulation, nor were any directional differences in the optokinetic responses evident Figure 9 shows optokinetic nystagmus recordings

nystagmus to the left but with the head lowered the same stimulus produced nystagmus to the right

Some animals yielded no recorded nystagmus to either stimulus when the head was tilted downward However, of the cats which did react a definite directional difference appeared These animals had been habituated to a stimulus provoking nystagmus to the left when the same stimulus was administered with the head lowered a vigorous response to the right was obtained When the temperatures were interchanged a reduced response in the habituated direction was elicited The latter phenomena were also observed by Proctor and Fernandez (1963) who noted in support of the notion that habituation is of central origin that the mechanism underlying habituation is operating on the neural system which determines the direction of nystagmus (p 507) However the responses produced with the head down in this study differed in appearance from those of the upright position, that is the number of beats was greater and the amplitude was considerably lower This lowering of amplitude may have contributed to the above mentioned apparent absence of head down nystagmus from some animals

Another characteristic observed among groups receiving stimulation in alternating directions following habituation was the apparent influence of the order of stimulation on the magnitude of the response That is there appeared to be less difference in the subsequent tests between the responses of the habituated and unhabituated directions when the first irrigation produced nystagmus in the previously habituated direction Perhaps the novelty associated with the change of the head position served to heighten the first response elicited regardless of the direction However this difference was only relative the previously unhabituated direction uniformly yielded more vigorous responses

Double irrigations

Following habituation to 30 sec bilateral irrigations animals in group AII each received 2 double irrigations (simultaneous bilateral calorizations of 26°C for 30 sec) at the usual interstimulus intervals of 20 min With such stimulation the horizontal component of nystagmus is ordinarily abolished and a vertical nystagmus usually appears Since the horizontal component of the response had been subjected to unidirectional habituation the double irrigations were administered to determine whether the nystagmus so elicited would evince a horizontal component in the unhabituated direction No such directional effect appeared Animals variously gave random eye movements or weak (prolonged low velocity) responses in one direction or the other (some of which may have included a vertical component)

Following the double irrigations both directions were tested with 30 sec bilateral calorizations of 26°C and 50°C (the temperatures were interchanged to produce both directions of nystagmus) The order of presentation of the

Although secondary nystagmus was not observed on every trial (a period of approximately 5 min), animals frequently exhibited a response in the direction of the secondary reaction 10–15 min after a stimulation, during the recording of the response of another animal (animals were tested in pairs). These late reactions (some of which may have been induced spontaneous nystagmus) occurred without additional stimulation, after a 5 min period in illumination and ranged from a "strong" response (Fig. 10) to only one beat every 5–7 seconds. The response shown in Figure 10 is the most vigorous of all the observed reactions of this type and therefore represents the extreme example.

Inverted primary nystagmus (a response in the opposite direction of the expected primary which appears prior to, or instead of, a response appropriate to the stimulus, Collins, 1963, Groen & Jongkees, 1949) was observed occasionally. Five animals exhibited occasional clear, though weak, inverted primary responses, in which the inverted beats were in evidence for 10–30 sec after termination of the irrigation. It is possible that these unusual responses are related to the delayed reactions noted above and depicted in Figure 10.

ZUSAMMENFASSUNG

Das Auftreten bilateraler kalorischer Nystagmusgewöhnung nach unilateraler Kalorisierung wurde an einer Gruppe von 60 Katzen untersucht. Gewöhnung an bilaterale kalorische Ohrspulungen verminderte deutlich die Reaktion auf sowohl schwächere als auch auf stärkere einseitige Reizung. Nachfolgende Untersuchungen vermittelten weitere Informationen in bezug auf die Wirkung kalorischer Gewöhnung an (1) Richtungsspezifität der Reaktion (2) Beibehaltung der Reaktionsabnahme und (3) optokinetischen Nystagmus.

Die statistische Analyse zeigte auch einen Geschlechtsunterschied im Ausmasse der Reaktionen.

REFERENCES

Collins, W. E., 1963. Observations on the elicitation of secondary and inverted primary nystagmus from the cat by unilateral caloric irrigation. *Aerospace Med.* 34, 1137.

— 1964 *a*. Nystagmus responses of the cat to rotation and to directionally equivalent and non-equivalent stimuli after unilateral caloric habituation. *Acta Otolaryng.* (Stockh.) 58, 247.

— 1964 *b*. Primary, secondary and caloric nystagmus of the cat following habituation to rotation. *J. Comp. Physiol. Psychol.* 57, 417.

Crampton, G. H., 1962. Directional imbalance of vestibular nystagmus in cat following repeated unidirectional angular acceleration. *Acta Otolaryng.* (Stockh.) 55, 41.

Dunlap, K., 1925. Adaptation of nystagmus to repeated caloric stimulation. *J. Comp. Psych.* 5, 485.

Edwards, A. L., 1960. *Experimental Design in Psychological Research.* New York: Holt, Rinehart and Winston.

Fernandez, C. and Schmidt, R., 1962. Studies on habituation of vestibular reflexes. II. Effect of caloric stimulation in decorticated cats. *Ann. Otol.* 71, 299.

Fluur, E. and Mendel, L., 1962 *a*. Habituation, efference and vestibular interplay. I. Monaural caloric habituation. *Acta Otolaryng.* (Stockh.) 55, 65.

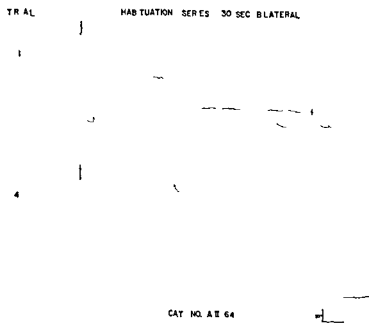


FIG. 10. Examples of inverse nystagmus. The tracings for trial 1 show vigorous primary and secondary reactions. The arrow indicates the start of secondary nystagmus; the jagged vertical line denotes a change of paper speed from 2.5 to 1.2 cm/sec. The tracing for trial 4 shows a brisk but reduced primary nystagmus; no secondary response appeared. Dots indicate the passage of approximately 10 min (including 5 min in illumination) after which, without benefit of any additional stimulus, a vigorous response in the direction of secondary nystagmus appeared. The latter was recorded in darkness while another animal was being tested (paper speed 2.5 cm/sec).

for both directions before and after vestibular habituation. The tracings show no differences in the form or quality of the responses from one condition to another.

Inverse responses

Two types of inverse vestibular responses were observed: secondary nystagmus and inverted primary nystagmus. Secondary nystagmus (a response following and in the direction opposite to the primary response) has been reported as a result of both rotatory and unilateral caloric stimulation in the cat (Collins 1964 *a, b*). In the present study, secondary reactions occurred frequently (322 trials) in the tracings of 51 cats. The magnitude of these reactions ranged from strong to very weak, and some of the latter may have represented induced spontaneous responses similar to those reported for man by Fluur & Mendel (1961 *b*).

The more intense stimuli appeared to elicit secondary responses more frequently, although there was no strict rank order relation observed between stimulus intensity and number of occurrences. Fewer secondary reactions occurred as the number of trials increased. This decline of secondary nystagmus has been reported in recent studies of the cat for both rotatory and unilateral caloric stimulation (Collins 1964 *a, b*), but is not reported to occur in man (Fluur & Mendel 1962 *a, b*).

ON THE BEHAVIOUR OF THE MICROPHONIC EFFECT OF THE COCHLEA DURING HYPOTHERMIA. AN EXPERIMENTAL STUDY

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The behaviour of the cochlear microphonic effect in animals subjected to gradual body cooling without previous barbiturate narcosis has been studied. The hypothermia, in some cases, has even reached a level of 13.5°C. It has been shown that close connections exist between the degree of temperature and therefore between body metabolism and the amplitude of the cochlear microphonic effect caused by sound stimulations of constant intensity. In our experimental animals it has been possible with subsequent body warming to obtain the return of the microphonic potentials to the pre-experimental level. The auricular apparatus in mammals is therefore capable of tolerating a very high degree of hypothermia without functional damage.

The behaviour of certain functions during body cooling has been examined in recent years by many research workers. The results obtained are interesting both from the theoretical as well as the practical point of view. It is important to understand the mechanism by which the functional changes occur during hypothermia, if this process must be applied more easily and with less risk in the treatment of certain diseases and during surgical operations on the heart and nervous system.

Previous workers, beside the circulatory and the respiratory systems, have investigated the activity of the central nervous system and of sensory organs at various levels of hypothermia.

As far as the function of the labyrinth is concerned, it has been established that the reactions to rotation stimuli are increased at a certain temperature level—(29–27°C in guinea pigs and rabbits, 25–24°C in monkeys). At lower temperatures the amplitude and duration of reactions are reduced, the rapid phase of nystagmus disappears at 24–23°C, while the slow phase is still present down to a temperature of about 20°C (Innocenti, 1941).

In a series of experiments carried out on animals under hypothermia with thermic and galvanic stimulation of the labyrinth, and by the study of otolithic reflexes, Menzio & Giulio (1951–1953) have been able to demonstrate that there exists a critical temperature (20–21°C) at which there is a functional arrest of the activity of the ampullar and macular receptors in the labyrinth (cold anaesthesia). On the other hand the activity of the

— 1962 *b* Habituation efference and vestibular interplay II *Combined caloric habituation* *Acta Otolaryng* (Stockh) 55 136

Griffith C R 1920 The organic effects of repeated bodily rotation *J Exp Psychol* 3 15

Groen J J., and Jongkees L B W., 1949 The measurement of the temperature at the eardrum during the caloric test of the labyrinth *J Physiol* *108* 35

Guedry, F I 1964 Psychophysiological studies of vestibular function In W D Neff (Ed) *Advances in Sensory Physiology* New York Academic Press

Halstead W C., 1935 The effects of cerebellar lesions upon the habituation of post rotational nystagmus *Comp Psychol Monog* *12* 1

Henriksson N G 1956 Speed of slow component and duration in caloric nystagmus *Acta Otolaryng* (Stockh) Suppl *125* 20

Henriksson N G., Fernandez C., and Kohut R I., 1961 The caloric test in the cat *Acta Otolaryng* (Stockh) 53 21

Henriksson N G Kohut R I and Fernandez C 1961 Studies on habituation of vestibular reflexes I Effect of repetitive caloric test *Acta Otolaryng* (Stockh) 53 333

Hood J D and Pfaltz C R 1954 Observations upon the effects of repeated stimulation upon rotational and caloric nystagmus *J Physiol* *124* 130

Maxwell S S., Burke U L., and Reston C 1922 The effect of rotation on the duration of after nystagmus in the rabbit *Amer J Physiol* 58 432

Proctor L R., and Fernandez C 1963 Studies on habituation of vestibular reflexes IV Effect of caloric stimulation in blindfolded cats *Acta Otolaryng* (Stockh) 56 500

Ward P H., and Fernandez C 1963 Experimental studies on vestibular mechanisms I Directional preponderance of nystagmus in cats *Ann Otol* 72 507

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of the changes has been observed The authors have noted finally that in the course of hypothermia, the changes in the cochlear microphonic effect and action potentials produced by asphyxia are less marked

As referring to the c m effect results similar to those of Fernandez Singh & Perlman have been obtained by Gulick & Cutt (1960) however, according to these authors a return of the cochlear response to the control state occurs only when the hypothermia does not go below 30°C If the animals are taken to a lower temperature level (particularly to 25–24°C) changes of cochlear microphonic effect are not completely reversible

It is evident from the literature that there is almost complete agreement by the various authors even in different animals on the observations made during the reduction of temperature However, opinions are notably different on the behaviour of the cochlear microphonic effect during the return to normal temperature according to Fernandez and colleagues these changes are reversible even when the hypothermia has been taken down to 20 C but according to Gulick and Cutt the changes become permanent if the hypothermia reaches 23°C

These differences may be due to the time taken to cool the body Fernandez and colleagues in fact took 45 minutes to take the guinea pig temperature from 38 to 20°C while in the experiments performed by Gulick and Cutt a temperature of 26 or 23°C was reached only after a period of two or three hours Another noteworthy fact is the type and depth of anaesthesia nearly all the authors who have been quoted have used more or less large quantities of barbiturates administered endoperitoneally However, it is to be noted that this type of anaesthesia by itself produces a reduction in the temperature to such an extent that some authors have had to warm the animals in order to start the experiment from a temperature level of 37 38°C

These points not being sufficiently clear and due to the increasing use of hypothermia in clinical practice we have undertaken a research concentrating our efforts to try and discover whether hypothermia applied without previous general anaesthesia and therefore without previous depression of the nerve centres would enable us to study these phenomena even at very low body temperatures with the possibility of recovery of the experimental animal

The experiments have been performed on guinea pigs of both sexes weighing between 400 and 500 g Under light ether narcosis the *Bulla* has been opened by the epitympanic route and a silver electrode inserted into the basal loop of the cochlea After the effect of the anaesthetic had worn off and the state of the circulation respiration and the temperature of the animal had been controlled we proceeded with the cooling placing the body (excluding the head) in a bath of water progressively lowering the temperature During the whole course of the experiment the temperature was controlled rectally so that it was lowered slowly and gradually about 1 C every 4 to 5 minutes

nervous centres involved in the vestibular reflex ceases at a lower temperature level. This fact represents the first documentation of the greater sensibility to anaesthesia by cooling of certain receptors as compared to the central nervous system.

With reference to the function of the cochlea during hypothermia the microphonic effect of the cochlea and the action potentials of the auditory nerve have been the objects of study. Adrian, Bronk & Philips had already observed in 1931 that in experimental animals the reduction in temperature of the cochlea reduces the amplitude of the cochlear microphonic effect.

Later Kahana, Rosenblith & Galambos (1950) showed that in the hamster a progressive reduction in the temperature from 30 to 18°C does not provoke modification in the latent period but causes a notable reduction in the amplitude of the cochlear microphonic effect (as much as 30% of the initial value).

Several years later Bornschein & Krejci (1955) observed in the guinea pig that localized cooling of the ventral surface of the cochlea at the level of 2nd, 3rd and 4th loops produces a noticeable reduction in the cochlear microphonic effect that can be detected in the basal loop. These authors have also observed that the changes in the cochlear microphonic effect produced by acute anoxia are different in hypothermia from those observed at normal temperatures.

Finally, it has been noted that when the temperature is brought back to the control values changes occur in the type of waves and in the phase of microphonic effect.

Chambers & Lucchina (1960) have observed, with localised cooling in different points in the cochlea of a cat, different effects on the cochlear potentials according to the site of cooling and the frequency of the sonorous stimulations.

Fernandez, Singh & Perlman (1958) have shown that in guinea pigs under narcosis the gradual body cooling from 38 to 20°C does not alter the latent period but produces a raising of the threshold and a corresponding reduction in the amplitude of the cochlear microphonic effect. A study of the action potentials produced under the same experimental conditions has confirmed that besides raising of the threshold and the reduction in amplitude there is an increase in the latent period, which, in fact, measured from the beginning of the cochlear microphonic effect to the negative peaks N and N increases respectively by 1.3 and 2.3 m secs.

The relationship existing between the reduction in temperature and the reduction in amplitude of the cochlear microphonic effect and the action potential is a direct one at all the frequencies examined (from 700 to 10 000 cycles). A linear correlation also exists between temperature fall and the raising of the threshold of the microphonic effect. This correlation is less obvious as far as the increase of the threshold of the action potential is concerned.

During the return to normal temperature in the

of the changes has been observed The authors have noted finally that in the course of hypothermia, the changes in the cochlear microphonic effect and action potentials produced by asphyxia are less marked

As referring to the c m effect results similar to those of Fernandez Singh & Perlman have been obtained by Gulick & Cutt (1960) however according to these authors a return of the cochlear response to the control state occurs only when the hypothermia does not go below 30°C If the animals are taken to a lower temperature level (particularly to 25–24°C) changes of cochlear microphonic effect are not completely reversible

It is evident from the literature that there is almost complete agreement by the various authors even in different animals on the observations made during the reduction of temperature However, opinions are notably different on the behaviour of the cochlear microphonic effect during the return to normal temperature according to Fernandez and colleagues these changes are reversible even when the hypothermia has been taken down to 20°C but according to Gulick and Cutt the changes become permanent if the hypothermia reaches 23°C

These differences may be due to the time taken to cool the body Fernandez and colleagues in fact took 45 minutes to take the guinea pig temperature from 38 to 20°C, while in the experiments performed by Gulick and Cutt a temperature of 26 or 23°C was reached only after a period of two or three hours Another noteworthy fact is the type and depth of anaesthesia nearly all the authors who have been quoted have used more or less large quantities of barbiturates administered endoperitoneally However, it is to be noted that this type of anaesthesia by itself produces a reduction in the temperature to such an extent that some authors have had to warm the animals in order to start the experiment from a temperature level of 37 38 C

These *points not being* sufficiently clear and due to the increasing use of hypothermia in clinical practice we have undertaken a research concentrating our efforts to try and discover whether hypothermia applied without previous general anaesthesia and therefore without previous depression of the *nerve* centres would enable us to study these phenomena even at very low *body* temperatures with the possibility of recovery of the experimental *animal*

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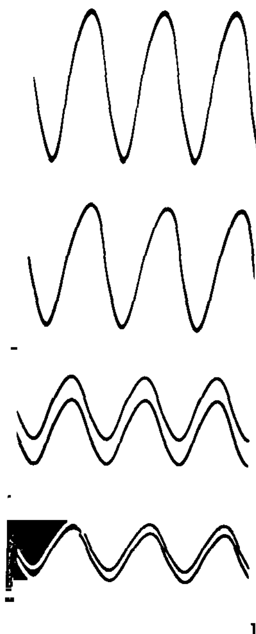


FIG 1 Behaviour of the amplitude of the cochlear potential in an adult guinea pig (n 4) subjected to gradual hypothermia Readings taken at body temperatures between 38°C and 17°C

In the first group of experiments the body temperature of the animals was reduced only to 20–22°C, in a second group however, the hypothermia was taken to 16, 15 and even to 13 5°C

Twenty-six guinea pigs have been studied, in only two cases (with body temperatures of 18 and 14°C) was it not possible to recover the animals, owing to respiratory and circulatory insufficiency

The electrode inserted into the basal loop was connected to a pre-amplifier

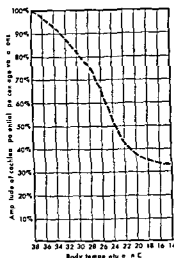


Fig 2 Percentage variations in the amplitude of the cochlear potential in an adult guinea pig (n 4) subjected to gradual hypothermia compared with the reduction in body temperature

and this in turn was connected to a cathode ray oscillograph with two channels and registration obtained with microfilm

The ear was stimulated with pure tones with frequencies of 1000, 2000, 3000 and 4000 cycles per second, by means of a small loud-speaker in fixed contact with the external orifice of the sound conductor so that the intensity of the stimulating sound remained constant

RESULTS

In the first phase of body cooling, during which the temperature went down from 38 to 34°C, a progressive diminution in the amplitude of the cochlear microphonic effect was observed, which was not always constant in all the experimental animals In some of these, the diminution in amplitude was, at first, of moderate proportions and became more evident only when the temperature reached 35 34°C In other cases, however, the reduction was manifest immediately after the beginning of cooling showing the same course, which is characteristic at the lower temperature levels

At temperatures below 34°C the reduction in the cochlear potential becomes progressively more obvious, with an almost direct linear relationship between the heat reduction and the amplitude of the bio-electrical phenomenon (Figs 1 and 2) In some of the animals the same pattern is observed down to the lowest body temperature (17°C, see Figs 3 and 4) In other animals however, the reduction in amplitude of the microphonic effect is slightly less when the lowest temperature levels are reached

In the different animals studied by us the reduction in the amplitude of the microphonic potential is between 3 2 and 3 56% for every degree centi-

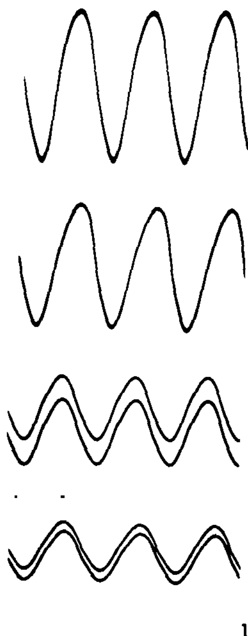


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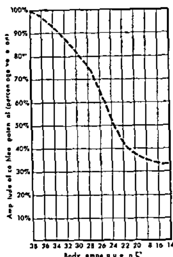


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Fig. 3. Behaviour of the amplitude of the cochlear potential in adult guinea pig (n. 11) subjected to gradual hypothermia: recordings taken at body temperatures between 38° C and 10° C.

grade of temperature reduction: thus at a temperature of 15-18° C the amplitude of the phenomenon is reduced to the 21-36% of the control values. In the course of the experiments we felt that this slight difference was the result of the different gradient of temperature reduction which, although slight, has been encountered in different animals. Beside reduction in amplitude at a body temperature below 26° C doubling of the tracing has been observed, as is well shown in Figs. 5 and 6.

This fact cannot be easily explained and it is probably due to technical factors. Splitting of the tracing was present almost constantly when the body temperature was very low.

A less linear behaviour has been observed during the return of the temperature to normal level. In the first experiments we had the impression that the cochlear potential, although presenting a noteworthy increase in

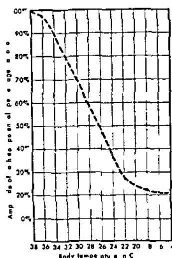
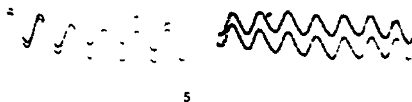


Fig 4 Percentage variations in the amplitude of the cochlear potential in an adult guinea pig (n 11) subjected to gradual hypothermia compared with the reduction in body temperature

amplitude while the temperature raised did not reach the levels observed before hypothermia was started

Further observations, carried out with a strict control of the temperature of the immersion water so that rewarming followed nearly the same course as the body cooling, have allowed us to observe a progressive increase in the amplitude of the microphonic effect Nevertheless it is not possible to observe a direct linear relationship between the heat increase and the amplitude of the bio electrical phenomenon At a temperature of 38 38.5°C the amplitude of the phenomenon as can be seen in Fig 7 is nearly the same as that observed before the beginning of the hypothermia However the complete return to the preoperative conditions takes place only when the body temperature reaches the level of 40–41 C



5 6

Figs 5 and 6 Registration of the cochlear potential in an adult guinea pig n 14 at a temperature of 23 C and 18 C doubling of the tracing



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functional condition) tolerate reasonably well very low body temperatures. It has been possible to bring the hypothermia to very low levels (as far as 13.5°C) studying for the first time the behaviour of the cochlear microphonic effect at temperatures below 18°C. In this way the progress of the microphonic potential has been examined during temperature changes of about 25°C (from 38 to 13.5°C), showing that the changes which determine the bio-electrical phenomenon are completely reversible. In fact, the gradual warming of the animal produces a progressive increase in the amplitude of the potentials which, in various cases (when the temperature returns to levels of 38–38.5°C) return to the same condition observed before cooling.

These observations are at variance with those of Gulick and Cutt, according to whom the modifications of the microphonic potentials are no longer reversible if the temperature falls below 23°C, but confirm the theories of Fernandez, Singh and Perlman who state that the changes are reversible even if the hypothermia is pushed down to 20°C. It may be of some interest, from the practical point of view, to note that in our method as with that of Fernandez, the reduction in temperature was induced in a much shorter time than by Gulick and Cutt.

In our experiments has also been confirmed the existence of a linear relationship between the reduction of the temperature and the decrease of the amplitude of the cochlear microphonic effect. It is therefore evident that the degree of the microphonic reaction produced by a sound of constant intensity is connected with body metabolism. The modifications in the energy exchanges produced in the animal by the variations in temperature are faithfully represented by the variations in the microphonic potential. Evidence of these functional connections seems to us particularly significant both from the theoretical and the practical points of view, because it shows the sensitivity of the organ of Corti to all the modifications and alterations of body metabolism.

RÉSUMÉ

Les auteurs ont étudié le comportement de l'e.m.c. sur des animaux soumis à perfrigération sans narcose barbiturique préalable. L'hypothermie dans certains cas a touché les 13.5°C. On a démontré qu'il existe un rapport direct entre le degré de refroidissement et par conséquent du métabolisme et l'amplitude de l'e.m.c. dû à des stimulations sonores d'intensité constante. Sur les animaux étudiés, avec le retour à la température normale on a pu obtenir le retour des potentiels microphoniques au niveau observé avant le début de l'expérience. L'appareil auriculaire des mammifères est donc en état de supporter sans dommage des hypothermies même profondes.

ZUSAMMENFASSUNG

Die Verfasser haben die Cochlearpotentiale bei Tieren während gradueller Verminderung der Körpertemperatur ohne Barbiturnarkose untersucht. Die Hypothermie gelang in einigen Fällen bis zu 13.5°C. Es wurde demonstriert, dass

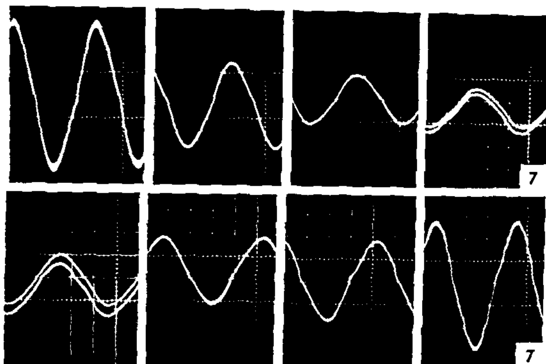


FIG. 7. Behaviour of the amplitude of the cochlear potential in a guinea pig subjected to gradual hypothermia and later warmed to normal body temperature.

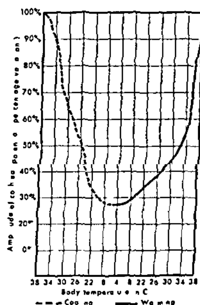


FIG. 8. Percentage variations in the amplitude of the cochlear potential in an adult guinea pig subjected to gradual hypothermia and later warmed to normal body temperature compared with the body temperature.

DISCUSSION AND CONCLUSION

Our observations enable us to solve some of the problems concerning the behaviour of the microphonic potential under certain experimental conditions. The guinea pigs subjected to gradual body cooling without previous barbiturate narcosis (therefore with the higher nervous centres in normal

functional condition) tolerate reasonably well very low body temperatures It has been possible to bring the hypothermia to very low levels (as far as 13.5°C) studying for the first time the behaviour of the cochlear microphonic effect at temperatures below 18°C In this way the progress of the microphonic potential has been examined during temperature changes of about 25°C (from 38 to 13 5°C), showing that the changes which determine the bio electrical phenomenon are completely reversible In fact, the gradual warming of the animal produces a progressive increase in the amplitude of the potentials which, in various cases (when the temperature returns to levels of 38–38 5°C) return to the same condition observed before cooling

These observations are at variance with those of Gulick and Cutt, according to whom the modifications of the microphonic potentials are no longer reversible if the temperature falls below 23°C but confirm the theories of Fernandez, Singh and Perlman who state that the changes are reversible even if the hypothermia is pushed down to 20°C. It may be of some interest from the practical point of view to note that in our method as with that of Fernandez the reduction in temperature was induced in a much shorter time than by Gulick and Cutt

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Les auteurs ont étudié le comportement de l e m c sur des animaux soumis a perfrigeration sans narcose barbiturique préalable L hypothermie dans certains cas a touché les 13 5 C On a demontre qu il existe un rapport direct entre le degre de refroidissement et par consequent du metabolisme et l amplitude de l e m c du à des stimulations sonores d intensite constante Sur les animaux etudiés avec le retour a la temperature normale on a pu obtenir le retour des potentiels microphoniques au niveau observé avant le début de l experience l appareil auriculaire des mammiferes est donc en etat de supporter sans dommage des hypothermies meme profondes

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enge Beziehungen zwischen Temperaturgrad beziehungsweise Energieumsatz und Grösse der Cochlearpotentiale nach Schallreizen konstanter Intensität bestehen. In den untersuchten Tieren ist es möglich gewesen, nach Körperwiedererwärmung die vorexperimentellen mikrophonischen Potentiale wiederzusehen. Wir können deswegen bestätigen, dass der Ohrenapparat der Säugetiere imstande ist, ziemlich tiefe Hypothermien ohne Funktionsstörungen zu vertragen.

REFERENCES

ADRIAN, D., BRONK, D. W. and PHILLIPS, G. 1931. *The nervous origin of the Wever and Bray effect. J. Physiol.* (Lond.), 73, 27.

BORNSCHEIN, H., and KREJCI, F. 1955. Elektrophysiologische Untersuchungen über Temperatureffekte in der Schnecke. *Acta Otolaryng.* (Stockh.), 45, 467.

CHAMBERS, A. H. and LUCCHINA, G. G. 1960. Effects on round window potentials of localized changes in cochlear temperature. *Ann. Otol.* 69, 698.

FERNANDEZ, C., SINGH, H. and PERLMAN, H. 1958. Effect of short term hypothermia on cochlear responses. *Acta Otolaryng.* (Stockh.) 49, 189.

GULICK, W. L., and COTT, R. A. 1960. *The effects of abnormal body temperature upon the ear: cooling. Ann. Otol.* 69, 35.

KAHANA, L., ROSENBLITH, W. A. and GALAMBOS, R. 1950. Effect of temperature change on round window response in the Hamster. *Amer. J. Physiol.* 163, 213.

INNOCENTI, M., 1941. Temperatura corporea e reazioni vestibolari. *Arch. Fisiol.* 41, 425.

MENZIO, P., and GIULIO, L., 1950 *a*. Sul diverso comportamento della soglia galvanica rispetto a quella termica e rotatoria nei riguardi della fase lenta e rapida del nistagmo. *Boll. Soc. Ital. Biol. Sper.* 26, 9.

— 1951 *b*. *Variazioni di temperatura del labirinto e del sistema nervoso centrale da irrigazione dell'orecchio medio della cavia. Boll. Soc. Ital. Biol. Sper.* 27, 29.

— 1951 *c*. Importanza della temperatura dei recettori vestibolari per l'estrinsecazione delle reazioni labirintiche. *Boll. Soc. Ital. Biol. Sper.* 27, 31.

— 1951 *d*. Ricerche sull'attività dei recettori vestibolari. Recettori maculari e posizioni oculocompensatorie. *Boll. Soc. Ital. Biol. Sper.* 27, 1041.

— 1953. Ricerche sulla funzione dei recettori vestibolari. Comportamento dell'eccitabilità a basse temperature corporee. *Arch. Fisiol.* 53, 326.

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ACETYLCHOLINESTERASE ACTIVITY IN THE EFFERENT FIBERS OF THE STATO-ACOUSTIC NERVE

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Acetylcholinesterase activity was demonstrated histochemically in the efferent system of the VIIIth nerve. The distribution of the olivocochlear bundle was studied in decalcified temporal bones of cats. In addition to confirming the known course of the bundle, efferent fibers going to the apical and middle turn were seen in the cochlear nerve trunk. Similarly, the pathway of the vestibular efferent system was verified, but more fibers were localized than by previous investigations using other techniques. Selective transection of the efferent system to both divisions of the inner ear resulted in the loss of demonstrable enzyme activity.

INTRODUCTION

The course and distribution of the efferent nerve fibers of the inner ear have been established (Rasmussen, 1946 and 1953, Rasmussen & Gacek, 1958, Gacek, 1960). Most studies utilized the phenomenon of Wallerian degeneration of axons after strategic surgical lesions and employed myelin stains or silver impregnation to demonstrate these fibers. AChE activity has been localized histochemically in the efferent system within the brain stem, in the proximal portions of the VIIIth nerve (Rossi, 1961) and in the cochlear and vestibular endorgans (Dohlman, Farkashidy & Salonna, 1958, Vinnikov, 1958, Schuknecht, Churchill & Doran, 1959; Ireland & Farkashidy, 1961, Rossi, 1961, Hilding & Wersäll, 1962, Rossi & Cortesina, 1962). Because of technical difficulties imposed by the petrous bone, the course of cholinergic fibers could not be traced throughout the entire length of the VIIIth nerve in these studies.

In the present histochemical study, AChE activity has been demonstrated in the efferent nerve fibers of previously decalcified petrous bones. In normal and experimental animals we were able to point out hitherto unrecognized features of the cochlear and vestibular efferent system in the peripheral portion of the stato-acoustic nerve.

This study was supported by Research Grant NB 04135-03 of the National Institute of Neurological Diseases and Blindness, U.S. Public Health Service.

Abbreviations: AChE, Acetylcholinesterase; EDTA, disodium salt of ethylenediamine ... lear (bundle)

MATERIAL AND METHODS

Five healthy young adult cats were used. The posterior fossa was exposed by craniotomy and the root of the vestibular nerve was transsected dorsomedial to the descending trigeminal root. Thus all the cochlear and vestibular efferents to one ear were sectioned without damaging the blood supply to the inner ear. The opposite ear served as a control. Two of the experimental animals survived 8 and 9 days. The remaining three animals lived 19, 30 and 48 days respectively. The animals were sacrificed by an overdose of Nembutal.

Technique

After decapitation brain stems and inner ears were immediately removed. The petrous bones were put into a cold (4°C) solution of EDTA buffered at pH 7.4 (Balogh & Nomura, 1964). The bones were decalcified in 30 to 40 days. Then the petrous bones were cut serially at 20 μ with a rotary microtome in a cryostat at -18°C. The frozen sections were mounted on clean coverslips, thawed briefly, dried and kept in a cold room overnight. The sites of AChE activity were demonstrated by using the acetylthiocholine iodide method as modified by Gomori (Pearse 1961). After incubation at 37°C for 60 minutes the sections were rinsed in 3 changes of a saturated sodium sulphate solution. Then the sections were treated with dilute yellow ammonium sulfide, washed briefly and fixed with 10% formalin. The sections were mounted with Kaiser's glycerol jelly.

Control sections to rule out nonspecific reaction were incubated in a solution from which acetylthiocholine iodide was omitted but were otherwise treated identically. In some instances sections were preincubated for 30 minutes in a solution containing eserine (final concentration of 10^{-5} M) as a specific inhibitor of AChE activity.

Brain stems were also frozen on dry ice and sectioned serially to demonstrate AChE activity in them.

RESULTS

Dark brown copper sulfide was precipitated at the sites of AChE activity. It was consistently demonstrated in the intact OC bundle along its entire course. Preincubation in eserine completely inhibited the histochemical reaction.

Cochlear efferent fibers

The intact OC bundle as it courses over the descending trigeminal root in the outgoing vestibular nerve is demonstrated in Fig. 1. The parent efferent bundle proximal to Scarpa's ganglion is illustrated in Fig. 2. The areas of the saccular ganglion where the efferent cochlear neurons leave the vestibular nerve and travel via Oort's anastomosis to enter the cochlea



Fig. 1. Normal cat. Cross section of medulla oblongata. Sites of AChE activity appear black. Arrow indicates OC bundle in the vestibular nerve root. — V. Descending trigeminal root, *VII* genu of facial nerve. *ASO* accessory superior olivary nucleus, *CN*, cochlear nucleus. *RB* restiform body, *SO* superior olivary nucleus.



Fig. 2. Sites of AChE activity in the normal inner ear. Notice the position of the parent efferent nerve bundle (*EFF*) in the vestibular nerve. — *VII* Facial nerve. *CN* cochlear nerve. *IGSB* intraganglionic spiral bundle, *PI* pars intermedia. *VN* vestibular nerve.

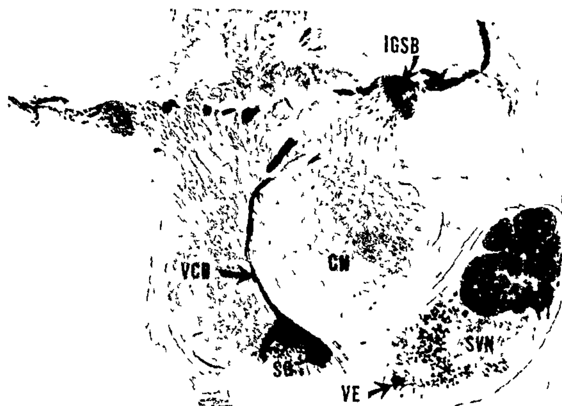


FIG. 3. Section of inner ear, distal to the level shown in Fig. 2. — *VII*, Facial nerve, *CN*, cochlear nerve, *IGSB*, intraganglionic spiral bundle, *PI*, pars intermedia, *SG*, saccular ganglion, *SVN*, superior division of vestibular nerve, *VCB*, vestibulocochlear (Oort's) bundle, *VE*, vestibular efferents.

are shown in Fig. 3. The intraganglionic spiral bundles gave off regularly efferent fibers to the organ of Corti (Fig. 4). In all specimens, the trunk of the cochlear nerve contained scattered efferent fibers. These numbered approximately 20 to 30 and they could be traced to the endorgan of the upper middle and apical turns (Fig. 5).

Vestibular efferent fibers

These nerve fibers course with the cochlear efferents in the parent bundle (Fig. 2). Near Scarpa's ganglion, however, the two bundles separate. At this point 2 or 3 fascicles and many scattered fibers diverge from the parent bundle and course in the superior division of the vestibular nerve (Figs. 3 and 4). More distally, these fascicles break up into individual scattered fibers which distribute to the endorgans of the superior division.

The efferent fibers innervating the posterior crista and the saccular macula leave the parent bundle as individual scattered fibers (Figs. 4 and 6) to run with their respective nerves.

Transected cochlear efferent fibers

In 5 animals the efferent supply to one ear was completely transected. Marked differences were seen in the distribution of AChE activity between

Fig. 4. Inner ear distal to saccular ganglion. Notice an efferent fiber in the cochlear nerve (arrow). Abbreviations as in Fig. 3.



Fig. 5. Scattered efferent fibers in the cochlear nerve trunk demonstrating AChE activity (arrows). — SpG: Spiral ganglion cells.

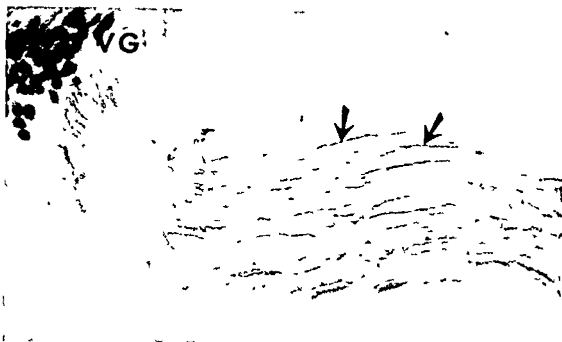


Fig. 6. Relatively many efferent fibers travel in the posterior ampullar nerve (arrows). — VG: Vestibular ganglion.

the operated and control ears. The degree of loss of enzyme activity varied with the length of survival after surgery. 8 and 9 days after transection Wallerian degeneration was seen in the axons of the OC system (Figs. 7 and 8). In comparison with the normal side, markedly decreased enzyme activity was indicated by light brown droplets in the degenerating axons. The more peripheral portions of the degenerating fibers could not be demonstrated. Nineteen to 48 days following transection no AChE activity or axonal debris was observed along the entire course of the efferents on the operated side, while the contralateral nerves demonstrated normal enzyme activity (Figs. 9 and 10). No enzyme activity was seen in the apical efferent fibers running within the cochlear nerve trunk; these fibers were also degenerated (Fig. 10).

Transected vestibular efferent fibers

Complete vestibular nerve section caused degeneration of the vestibular efferent system. Eight and 9 days after transection, lightly stained droplets outlined the degenerating axons. As with the cochlear efferent fibers enzyme activity in the more distal segments in the vestibular axons could not be demonstrated. Nineteen to 48 days after surgery enzyme activity was completely absent in any portion of the vestibular nerve or its branches (Figs. 11 *a* and *b*).

DISCUSSION

In this study AChE activity was demonstrated in the efferent system along the entire course of the VIIIth nerve. Effective histochemical localiza-

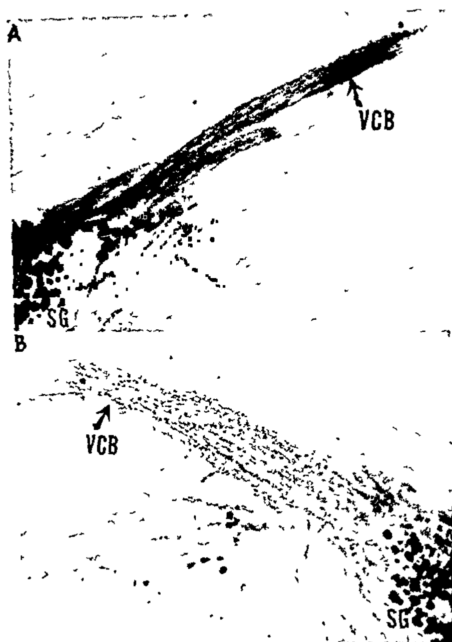


Fig. 7. Efferent cochlear fibers in Oort's anastomosis showing AChE activity. (A) Normal ear. (B) Contralateral ear eight days after transection of the OC bundle. Enzyme activity is diminished *in the debris of degenerated fibers*. SG, Saccular ganglion; VCB, vestibulocochlear (Oort's) bundle.

[illegible] of AChE activity was possible in petrous bones that were decalcified with cold EDTA. The technical aspects of decalcification and histochemical demonstration of AChE activity have been described elsewhere (Balogh, 1962; Balogh & Nomura, 1964).

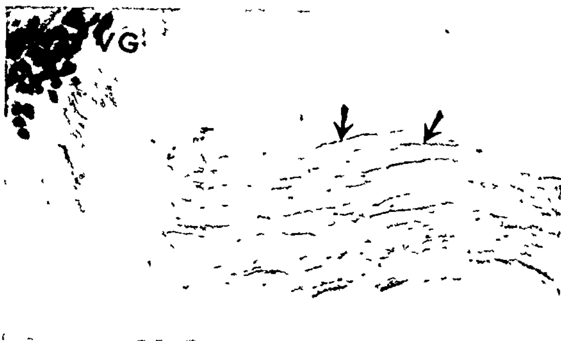


Fig. 6. Relatively many efferent fibers travel in the posterior ampullar nerve (arrows). — VG: Vestibular ganglion.

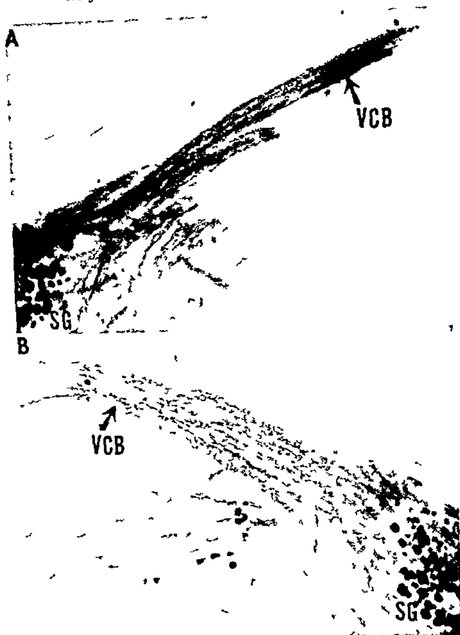
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Fig. 8. Same animal as in Fig. 7. (A) Normal ear showing strong AChE activity in the spiral portion of the OC bundle. (B) Contralateral ear with diminished enzyme activity in the degenerating OC fibers. *SpB* Spiral OC bundle. *SpG* spiral ganglion.

The efferent fibers can be selectively demonstrated in this manner. The histochemical technique localizes the course and distribution of the intact efferent system in the petrous bone. Other methods can only visualize it by the products of Wallerian degeneration after nerve transection. Extremely fine unmyelinated or thinly myelinated fibers in both divisions of the VIIIth nerve within the petrous bone may escape demonstration by the conventional methods.

In their histochemical study, Schuknecht, Churchill & Doran (1959) recognized that the efferent cochlear nerve endings contain substantial amounts *of acetylcholinesterase activity which disappeared after efferent nerve tran*



Fig. 9. Cross section of medulla oblongata 48 days after complete unilateral transection of efferent fibers and facial nerve. No enzyme activity could be demonstrated in the OC bundle on the operated (left) side. Normal AChE activity is present in the opposite OC bundle (arrow). — V Descending trigeminal root. *VII* facial nerve. *ASO* accessory superior olivary nucleus. *CN* cochlear nucleus. *L* to *L* surgical lesion. *SO* superior olivary nucleus. *VN* vestibular nerve root.

section. Other histochemical investigations were limited to either the end-organ (Dohlman, Farkashidy & Salonna 1958, Vinnikov, 1958, Ireland & Farkashidy, 1961, Rossi, 1961, Hilding & Wersäll, 1962, Rossi & Cortesina, 1962) or the brain stem (Rossi & Cortesina 1962).

With our technique, AChE activity was specifically visualized in the efferent system of the cat. The observed histochemical pattern fits the classical description of the cochlear and vestibular efferent systems (Rasmussen 1946, 1953, Gacek 1960). Selective transection of the efferent neurons resulted in a loss of AChE activity.

Several new findings were revealed in this study. We could observe efferent fibers entirely within the cochlear nerve trunk traveling toward the upper middle and apical turns of the cochlea. These fibers emerged from the ventrolateral aspect of the ventral cochlear nucleus and were found in that portion of the cochlear nerve which supplies the apical and upper middle turns of the cochlea. These efferent fibers numbered about 20 to 30, were of small diameter (less than 1 μ) and failed to stain after selective transection of the OC bundle sparing the cochlear nuclei. It follows that these apical and middle turn cochlear nerve effferents are a part of the OC system. It is possible that these are the peripheral extensions of fibers which leave the OC bundle as it passes beneath to the ventral cochlear nucleus. Many of these fibers ended about cells in the ventrolateral cochlear nucleus, while others could not be traced to their termination by Rasmus-

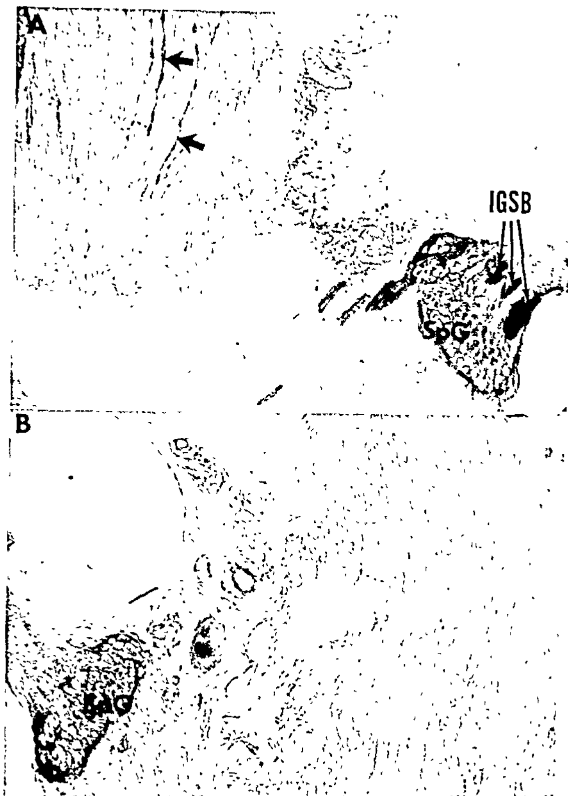


FIG. 10. Spiral ganglion of the middle turn with apical efferents. Same animal as in Figure 9. (A) Normal ear showing strong AChE activity in the intraganglionic spiral bundles (IGSB) and in the scattered apical efferents (heavy arrows) of the cochlear nerve. (B) Operated side with complete loss of demonstrable enzyme activity in the IGSB and the apical efferent fibers. — *SpG*, Spiral ganglion

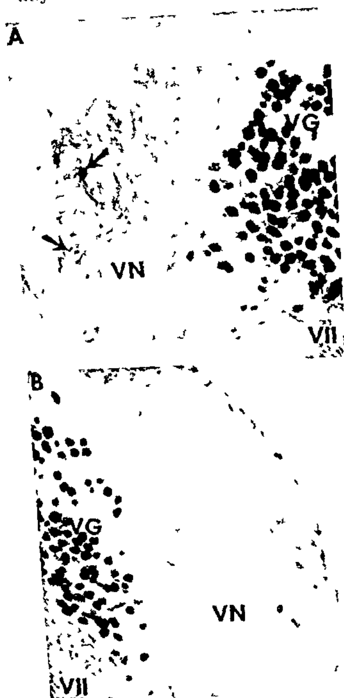


Fig. 11. Ganglion (VG) of the superior division of the vestibular nerve (VN). (A) Normal ear with AChE activity in the scattered vestibular efferent fibers (arrows). (B) Operated side showing no enzyme activity in the transected efferent fibers. — *VII* Facial nerve.



Fig. 10. Spiral ganglion of the middle turn with apical efferents. Same animal as in Figure 9. (A) Normal ear showing strong AChE activity in the intraganglionic spiral bundles (IGSB) and in the scattered apical efferents (heavy arrows) of the cochlear nerve. (B) Operated side with complete loss of the acetylcholinesterase enzyme activity in the IGSB and the apical efferent fibers. — SpG, Spiral ganglion.

— 1960 Efferent fibers of the cochlear nerve and cochlear nucleus In G L Rasmussen and W F Windle *Neural Mechanisms of the Auditory and Vestibular Systems* Chapter 8, 105 Charles C Thomas Springfield, Illinois

Rasmussen G L, and Gacek R R, 1958 Concerning the question of an efferent fiber component of the vestibular nerve of the cat *Anat Rec*, *130* 361

Rossi, G, 1961 L'acétylcholinestérase au cours du développement de l'oreille interne du cobaye *Acta Otolaryng* (Stockh), Suppl *170*

Rossi G, and Cortesina G, 1962 Il "sistema efferente colinergico cocleo—vestibolare Sintesi storico—bibliografica e ricerche personali *Minerva Otorinolaring* *12* 173

Schuknecht H F, Churchill, J A, and Doran, R, 1959 The localization of acetylcholinesterase in the cochlea *AMA Arch Otolaryng* *69* 549

Smith C A, and Rasmussen G L, 1963 Recent observations on the olivo-cochlear bundle *Ann Otol* *72* 489

Vinnikov Ya A, 1958 Histochemical investigation of receptors structures (maculae and cristae ampullares) of the vestibular part of the labyrinth in mammals (Russian text) *Doklady Akad Nauk SSSR* (Moscow) *122* 1111

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sen (1960). It is entirely possible that these fibers may pass through the nucleus and into the cochlear nerve.

Afferents from the apical turn go to the area of the ventral cochlear nucleus which is associated with these fibers. No attempt was made here to study AChE activity in the organ of Corti or in the spiral ganglion cells; this has been amply demonstrated by others.

The course and distribution of the efferent vestibular system as originally described by Gacek (1958, 1960) was confirmed by the present investigation. We found that these fibers were more numerous than previously thought, numbering about 400. Moreover, the efferent vestibular fibers branch as they course peripherally in the individual vestibular nerve rami.

The finding of a greater number of efferent vestibular fibers is perhaps due to inability of myelin stain and silver impregnation to demonstrate many of the smaller fibers.

ZUSAMMENFASSUNG

Eine beträchtliche Aktivität von Acetylcholinesterase konnte in den efferenten Bahnen des Nervus statoacusticus histochemisch nachgewiesen werden. Die Fasern des olivocochlearen Bündels wurden im entkalkten Os temporale von Katzen untersucht. Es gelang, die efferenten Fasern ihrem bekannten Verlauf entlang zu den apikalen und mittleren Windungen der Cochlea zu verfolgen. Die efferenten Bahnen des Nervus vestibularis wurden gleicherweise dargestellt, wobei mehr efferente Fasern entdeckt wurden, als bisher vermutet. Nach Durchtrennung der efferenten Bündel von beiden Teilen des VIII. Hirnnerven kommt es zu einer histochemisch nachweisbaren Herabsetzung der Acetylcholinesteraseaktivität.

REFERENCES

Balogh, K., Jr. 1962. Decalcification with Versene for histochemical study of oxidative enzyme systems. *J Histochem Cytochem 10*: 232.

Balogh, K., Jr., and Nomura, Y. 1964. A technique for the demonstration of acetylcholinesterase activity in the inner ear after decalcification with EDTA. *J Histochem Cytochem 12*: 931.

Dohlman, G., Farkashidy, J., and Salonna, F. 1958. Centrifugal nerve fibers to the sensory epithelium of the vestibular labyrinth. *J Laryng 72*: 984.

Gacek, R. R. 1960. Efferent component of the vestibular nerve. In G. L. Rasmussen and W. F. Windle: *Neural Mechanisms of the Auditory and Vestibular Systems*, Chapter 20, 276. Charles C Thomas, Springfield, Illinois.

Hilding, D., and Wersäll, J. 1962. Cholinesterase and its relation to the nerve endings in the inner ear. *Acta Otolaryng* (Stockh) 55: 205.

Ireland, P. E., and Farkashidy, J. 1961. Studies on the efferent innervation of the vestibular end organs. *Ann Otol 70*: 490.

Pearse, A. G. E. 1961. *Histochemistry, Theoretical and Applied.* Little, Brown and Company, Boston.

Rasmussen, G. L. 1946. The olivary peduncle and other fiber projections of the superior olivary complex. *J Comp Neurol 84*: 141.

— 1953. Further observations of the efferent cochlear bundle. *J Comp Neurol 99*: 61.

— 1960 Efferent fibers of the cochlear nerve and cochlear nucleus In G L RASMUSSEN and W F WINDLE Neural Mechanisms of the Auditory and Vestibular Systems Chapter 8 105 Charles C Thomas Springfield Illinois
RASMUSSEN G L., and GACEK R R., 1958 Concerning the question of an efferent fiber component of the vestibular nerve of the cat Anat Rec, 130, 361
ROSSI, G., 1961 L acetylcholinesterase au cours du developpement de l oreille interne du cobaye Acta Otolaryng (Stockh), Suppl 170
ROSSI G., and CORTESINA G., 1962 Il 'sistema efferente colinergico cocleo—vestibolare' Sintesi storico—bibliografica e ricerche personali Minerva Otorinolaring 12 173
SCHUKNECHT H F., CHURCHILL J A., and DORAN R., 1959 The localization of acetylcholinesterase in the cochlea AMA Arch Otolaryng 69 549
SMITH C A., and RASMUSSEN G L., 1963 Recent observations on the olivo cochlear bundle Ann Otol 72 489
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PERFORATIONS OF THE ESOPHAGUS

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The cases of perforation of the esophagus treated at the E.N.T. clinic of the Sahlgrenska hospital, Göteborg, Sweden, during the years 1950–1959 have been analyzed. During this period 2868 endoscopies of the esophagus have been performed. In all 31 cases of perforation were grouped in 13 preoperative, 7 operative small and 11 operative big. The last group included 3 cases of perforation of the stomach. These underwent laparotomy. Of the other 8 cases with big perforation 6 were treated conservatively and 2 underwent mediastinotomy. During the course of treatment only one patient died. However, the diagnosis was heart infarction. Therapeutically the authors recommend conservative treatment of esophagus perforations excluding those cases which show big perforations engaging neighbor organs.

In spite of the continuously increasing number of and more serious indications for esophagoscopy, perforation of the esophagus is a rare event in the routine work of an E.N.T. department. However, when it happens serious problems may arise. There are different opinions about the best treatment. Some authors recommend acute surgery in every case, while others are more conservative. The purpose of this report is to be a contribution to the continuous discussion of the problems associated with perforation of the esophagus.

MATERIAL

Our material comprises all the patients on which esophagoscopy has been performed during the period 1950–1959 at the E.N.T. department. In all 2868 esophagoscopies were performed, mostly on in-patients from the E.N.T. department, and other departments of the Sahlgrenska hospital and partly on a few out-patients.

The perforation cases have been grouped as "preoperative", i.e. when the patients presented, for example, with a perforation caused by a foreign body, and "operative", i.e. instrumental perforations. The latter group was further divided in "small" perforations, including those with so-called "pinhole perforations", and "big" perforations, including all other types.

TABLE 1 *All the cases of perforation from 2868 esophagoscopies*

Group	Number	Per cent
Preoperative	13	0 45
Operative, "small	7	0 24
Operative, 'big'	11	0 38
Total	31	1 07

RESULTS AND DISCUSSION

Of 2868 patients who have undergone esophagoscopy, 31 had perforations (Table 1) Thirteen of these were preoperative, i e caused by foreign bodies, 7 were instrumental "small" perforations and 11 classified as "big" instrumental perforations The frequency of perforations as a complication of esophagoscopy was 0 6% which agrees well with the frequency reported in other series (Elner & Dahlbäck, 1961)

The localization of the perforations is seen in Table 2 No less than 3 of 11 of the operative "big" perforations were ventricle perforations produced during probing of low located strictures The age distribution and indication for endoscopy are illustrated in Tables 3 and 4

In Table 5 the treatment, clinical course and duration of stay in hospital are shown All of the cases were given antibiotics In a small number only penicillin was given, but penicillin plus streptomycin were usually administered Conservative treatment only was given to all patients belonging to the preoperative- and operative "small" perforation groups In the group operative "big" perforations 5 of 11 patients were operated on, two underwent mediastinotomy, and the three patients with ventricle perforation un-

TABLE 2 *The localization of the perforations in the different groups*

	Pre operative	Operative 'small	Operative "big
Cervical	12	4	5
Upper thoracic	—	1	1
Lower thoracic	1	2	2
Abdominal	—	—	3
Total	13	7	11

TABLE 3 *The age distribution of the patients*

Age	0–10	11 20	21 30	31–40	41 50	51 60	61–70	71 80
Number	2			5	4	4	8	6

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*From the Department of Otolaryngology (Head Prof G Herberts)
University of Goteborg*

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In spite of the continuously increasing number of and more serious indications for esophagoscopy perforation of the esophagus is a rare event in the routine work of an E N T department However, when it happens serious problems may arise There are different opinions about the best treatment Some authors recommend acute surgery in every case, while others are more conservative The purpose of this report is to be a contribution to the continuous discussion of the problems associated with perforation of the esophagus

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The perforation cases have been grouped as "preoperative", i e when the patients presented, for example, with a perforation caused by a foreign body and "operative", i e instrumental perforations The latter group was further divided in "small" perforations including those with so-called "pinhole" perforations, and "big" perforations including all other types

patients, this would cover several decades Owing to the rapid development in medicine such a material would be too inhomogeneous Similar to other investigations on perforations of the esophagus our material therefore does not allow any categorical conclusions From this point of view the very low mortality reported here may be due to the smallness of the sample

In Scandinavian countries different kinds of anesthesia for esophagoscopy have been discussed In our series a combination of local anesthetics and pethidine have been used almost exclusively Only a few patients have been operated on under general anesthesia and muscle relaxation Local anesthetics in combination with pethidine do not seem to increase the risk of instrumental perforation General anesthesia gives the patient less discomfort during the endoscopy but more discomfort postoperatively Other factors, like the assessment of the individual case, the experience of the endoscopist, and the personal availability in the operating theatre, are of importance in the choice of anesthesia

The choice between conservative and surgical treatment is the most discussed problem in relation to perforation of esophagus In the investigations published during recent years, some authors treat small perforations conservatively and large perforations surgically (Chamberlain & Byerly, 1957, Doig, 1960, Mathewson, Chon & Schaupp, 1958, Sörensen & Welin, 1962) Other authors suggest that every perforation of the esophagus should be operated on (Rietz & Werner, 1959, Colman, 1958, Elner & Dahlbäck, 1961, Nealon *et al* 1961, Chladek, 1962) It is difficult to understand this categorical attitude as none of the reports permits a definite conclusion

When the perforation of the esophagus is caused by a foreign body or an instrument many factors may determine the clinical cource the size and localisation of the perforation, the injures of surrounding structures, the type and concentration of bacterial material, the condition of the mucous membrane within the area of perforation, the individual resistence to different strains of bacteria and the general condition of the patient Thus it is reasonable to suppose that even minute perforations under bad circumstances may lead to serious complications, while quite big perforations under good circumstances may heal without complications The paramount importance of clinical observation of patients with suspected perforations of the esophagus should be stressed

If the endoscopist realizes during the operation that the esophagus has been perforated involving pleura and lungs, there can be no doubt that acute surgical intervention is indicated If the diagnosis is not so certain expectance may be recommended The patient should be given big doses of broadspectrum antibiotics and parenteral or sond feeding and should be closely observed X-ray examination of the lungs, mediastinum and esophagus eventually using water soluble contrast medium should be performed The sedimentation rate and the white cell count should be followed If in spite of the therapy given, the condition of the patient deteriorates for about 6 hrs surgical intervention is required

TABLE 4. *The indication for the esophagoscopy*

	Pre operative	Operative small	Operative big
Foreign body	13	1	—
Achalasia	—	1	3
Diverticulum	—	1	3
Esophagitis	—	3	—
Neoplasm	—	1	1
Stricture	—	—	2
Hernia of the diaphragm	—	—	1
Congenital deformation	—	—	1
Total	13	7	11

derwent laparatomy. One of the patients died three days after the perforation. *The acute symptoms had ceased and she was to be operated on to make* a fistula to the stomach. During the onset of anesthesia she got cardiac arrest and died. The autopsy showed that she had recently a cardiac infarction which had not been diagnosed. Thus in the present series no death can be attributed to perforation of the esophagus. The length of the patients stay in hospital varied much. It is difficult to compare the mean value for the different groups, or to know which part of the stay in hospital was *caused by the perforation, and which part by the disease for which endoscopy was performed.* Neither can useful comparison be made between the mean stay in hospital for operated and non-operated patients. The two patients who underwent mediastinotomy were not operated on until 30 and 45 days *respectively after their perforations.*

With a total incidence of about 1% perforations of the esophagus caused instrumentally or by foreign bodies 3000 cases is statistically too small a *number, particularly if the material has to be divided into several groups* for certain conclusions to be drawn. It would be necessary to have at least 100 cases for complications, i.e. to base the investigation on about 10,000

TABLE 5. *Treatment and its outcome in the patients of the different groups*

The figures in the parentheses are the coefficient of variation

	Pre operative	Operative small	Operative big
Number of patients	13	7	11
Conservative treatment	13	7	6
Mediastinotomy			2
Laparotomy			3
Healed	13	7	10
Death			(1)
Days in hospital. Mean	9 (61%)	1[illegible] (80%)	39 (39%)

AIR INTAKE AND USAGE IN ESOPHAGEAL SPEECH

NOBUHIKO ISSHIKI and JOHN C SNIDECOR

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From the Department of Surgery Medical Center University of California Los Angeles and from the Department of Speech University of California Santa Barbara

Simultaneous recording of the rate and volume of oronasal air flow respiratory movement and voice signal were made on six esophageal speakers during speech swallowing and breathing Analysis of the data indicated the following

1 The method of air intake varied greatly with the individual A plosive injector charged most (91%) of his air during exhalation while four speakers who utilized the inhalation and injection methods insufflated more air without voice during inhalation than during exhalation

2 In all subjects except the plosive injector voice was produced predominantly with outward flow of air during exhalation

3 The mean flow rates for comfortably sustaining vowel /a ranged from 27 to 72 cc/sec

4 The inhalatory phonation was negligible for all speakers Swallowing was not effective for air intake

5 Some clinical implications of the experimental results and pneumotachographic method were discussed

INTRODUCTION

The first and most important step in learning esophageal speech is the act of taking air into the esophagus Because of its importance various methods of air insufflation have been investigated and discussed by many writers Historically the methods postulated are inhalation (suction) injection (tongue pumping) plosive injection and swallowing

The inhalation method is supported by Seeman (1958) Burger & Kaiser (1925) Brighton & Boone (1937) Froeschels (1951) and Hodson & Oswald (1958) According to the inhalation method air is sucked into the esophagus by (1) negative pressure in the esophagus created by the inhalatory movement and (2) simultaneous relaxation or opening of the pseudoglottis

The injection method on the other hand emphasizes the movement of the articulatory organs such as the tongue soft palate and mouth The air

This research was supported by USPHS Research Grant NB 04430 03 from the National Institute of Neurological Diseases and Blindness Research travel was supported by the Wood Glen Hall Research Fund

ZUSAMMENFASSUNG

Fälle mit Oesophagusperforation behandelt in der Ohrenklinik Sahlgrenska Sjukhuset Göteborg in den Jahren 1950–59 wurden analysiert. 2868 Oesophagoskopien wurden ausgeführt. Zusammengelegt 31 Fälle mit Perforation liessen sich in 13 praeoperative, 7 operative kleine und 11 operative grosse Fälle gruppieren. Zu der letzten Gruppe gehörten 3 Fälle von Ventrikelperforation, welche sämtlich akut operiert wurden. Von den restlichen 8 Fällen mit grosser operativer Perforation wurden 6 Fälle konservativ behandelt, während 2 Fälle einer Mediastinotomie unterzogen wurden. Im gesamten Material war im Laufe der Behandlungsperiode ein Todesfall zu verzeichnen. Die Todesursache war Herzinfarkt. In der Frage der Therapie schlossen sich die Verfasser einer konservativen Linie an mit Ausnahme der Fälle, bei denen eine grosse Perforation mit Beteiligung angrenzender Organe vorliegt.

REFERENCES

Chamberlain, J. M., and Byerly, W. G. 1957. Rupture of the esophagus. *Amer. J. Surg.* 93, 271.

Chládek, V. 1962. Current treatment of complicated esophageal perforations. *Česk. Gastroent. Vyž.* 16, 150.

Colman, B. H. 1958. Perforation of the hypopharynx and cervical oesophagus. *J. Laryngol.* 72, 970.

Doig, V. I. 1960. Perforated esophagus: an acute emergency. *Amer. J. Surg.* [illegible]0, 301.

Eisner, A., and Dahlbäck, O. 1961. Instrumental perforation of the esophagus. *Acta Otolaryng.* (Stockh.) 53, 279.

Mathewson, G., Jr., Chou, R., and Schaupp, W. C. 1958. Perforation of the esophagus. *Ann. Otol.* 67, 1141.

Nealon, T. F., Jr., Templeton, J. Y., Cuddy, V. D., and Gibbon, J. H., Jr. 1961. Instrumental perforation of the oesophagus. *J. Thor. Cardiov. Surg.* 41, 75.

Rietz, K. A., and Werner, B., 1959. Traumatic perforation of the esophagus. *Acta Chir. Scand.* 116, 401.

Sørensen, K., and Willis, L., 1962. Foreign bodies in the oesophagus. *Acta Otolaryng.* (Stockh.) [illegible], 308.

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INTRODUCTION

The first and most important step in learning esophageal speech is the act of taking air into the esophagus Because of its importance, various methods of air insufflation have been investigated and discussed by many writers Historically, the methods postulated are inhalation (suction), injection (tongue pumping), plosive-injection and swallowing

The inhalation method is supported by Seeman (1958), Burger & Kaiser (1925) Brighton & Boone (1937), Froeschels (1951) and Hodson & Oswald (1958) According to the inhalation method, air is sucked into the esophagus by (1) negative pressure in the esophagus created by the inhalatory movement and (2) simultaneous relaxation or opening of the pseudoglottis

The injection method, on the other hand, emphasizes the movement of the articulatory organs such as the tongue, soft palate and mouth The air

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in the closed glossopharyngeal cavity is pressed down (injected) into the esophagus chiefly by the downward and/or backward movement of the tongue. This phenomenon is variously described as "tongue pumping", "Pumpwerk", or "the initial stage of swallowing". Those who give general support to the injection method are Schilling (1927), Stetson (1937), van Gilse (1949) and Schlosshauer & Moeckel (1958). This method has recently been recommended by van den Berg, Moolenaar-Bijl & Damsté (1958). They also emphasize the importance of plosive consonants in esophageal speech. Gutzmann (1909) pointed out that the plosive consonants are most easily learned by the esophageal speaker. Furthermore, the significance of the plosive consonant was reevaluated by Moolenaar-Bijl ([illegible]) not only for the ease with which the plosive consonants can be produced, but also for their role in taking air into the esophagus. Most of the recent investigators appear to refute swallowing per se as a method of air intake in esophageal speech.

Methods of air intake and their respective proponents were classified as above for the sake of simplification. It should be mentioned, however, that definitions and opinions as to the method are different in detail depending on the investigators. For instance, Schlosshauer & Moeckel (1958), expressing their doubt about the conventional classification of method of air intake, stated that the combination of various methods would be consonant with the physiological mechanism available for esophageal speech. Based on the cineradiographic findings, Diedrich & Youngstrom (1962) reported that seven subjects used the inhalation method for trapping air and 20 subjects were classified as using the injection method.

Compared with the wealth of information regarding the method of air intake, very little work has been done in the actual measurement of air flow rate and volume for esophageal speech. [illegible] Kaiser (1926), using a [illegible] air volume recorder, studied the aerodynamic aspect of esophageal voice for the first time. She reported that an excellent esophageal speaker insufflated air generally a little less than 100 cc before speech. Based on the spirometric or radiographic findings, the volume of air per syllable or per word was reported by Stetson (1937), Howie (1947) and Snidecor (1962). Sugino (1962) stated that the air volume expired out of the esophagus ranged from 45 cc to 140 cc. So far as the available literature is concerned, no systematic and analytic measurement of air flow rate or its volume during esophageal speech appears to have been previously reported.

The present paper is one part of a series of three studies. The detailed description of an excellent esophageal speaker (W.) and the interrelationship between speech fluency and air flow characteristics are reported elsewhere. The topics discussed in this paper include: (1) individual variation in the method of esophageal speech; (2) advantage and disadvantage of each different method of air intake; (3) synchrony or asynchrony between the air intake and respiration; (4) synchrony or asynchrony between vocalization and respiration.

Fig 1 Diagram of the experimental arrangement

PROCEDURE

Subject Six male esophageal speakers were studied in the present investigation All of the speakers were intelligible and even the poorer speakers were judged as belonging in the automatic category described by Wepman *et al* (1953)

Tasks The tasks the subjects performed included reading a part of the Rainbow Passage sustaining phonations of the vowel /a/ counting as high as possible with one breath articulating CVC syllables swallowing and breathing The Rainbow Passage that the subjects read follows

When the sunlight strikes raindrops in the air they act like a prism and form a rainbow The rainbow is a division of white light into many beautiful colors These take the shape of a long round arch with its path high above and its two ends apparently beyond the horizon

Equipment An outline of the experimental arrangement is illustrated in Fig 1 Four measurements were made simultaneously during esophageal speech (1) the voice (2) respiratory (thoracic) movement (3) rate and (4) volume of air flow through the oronasal passage The subjects wore an air tight mask during speech so that no air could leak between the face and mask Voice signals were recorded on a tape recorder through a condenser microphone The output of the tape recorder was in turn connected via an AC amplifier to a four channel poly beam recorder to obtain an oscillographic recording of voice The movement of the thorax was recorded by means of a pneumograph A pressure variation in the pneumograph was sensitized by a strain gauge pressure transducer and recorded on another channel of the recorder

A pneumotachograph was utilized to measure the rate of air flow in and out of the mouth and nose during speech Electrical signals from the differential pressure transducer were amplified by a carrier amplifier and fed into one of the four channels of the poly beam recorder so that a tracing of the flow rate was secured An integrating amplifier converted the flow rate signal into the volume automatically The pneumotachograph was calibrated by frequent checks with a rotameter

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TABLE 1

Type	Direction of oronasal air flow	Phase relation between tracheal and oronasal air flow	Voicing or not	Remarks
1	In	Out phase	No	Indicative of injection of air
2	In	Out phase	Voice	Indicative of injection of air
3	In	In phase	No	Indicative of inhalatory intake
4	In	In phase	Voice	Inhalatory phonation
5	Out	Out phase	No	Loss of air or voiceless consonant
6	Out	Out phase	Voice	Asynchronous phonation
7	Out	In phase	No	Loss of air or voiceless consonant
8	Out	In phase	Voice	Synchronous phonation similar to normal

amount of outward flow of air On the other hand, all the outgoing air flow accompanied by voice was judged as emanating from the esophagus or from below the pseudoglottis

RESULTS

Total amount and rate of air intake

The total amount of air intake while reading the Rainbow Passage was about 1000 cc for each of the present subjects except for speaker P, as indicated by Table 2 The substantially smaller amount of air (325 cc) that

TABLE 2 *Air Intake*[a]

Ranking Subject	1 W	2 A	2 Y	3 C	3 M	4 P
Total volume of air intake in cc	948	1118	888	987	1189	325
Total speech time in sec	28	23	29	36	45	29
Rate of air intake in cc/sec	33 9	48 6	30 6	27 4	26 4	11 2
Synchronous intake of air (during inhalation) in volume percentage	76	9	62	64	71	44
Asynchronous intake of air (during exhalation)	24	91	38	36	29	56
Synchronous intake of air (during inhalation) in time percentage	66	16	48	49	64	43
Asynchronous intake of air (during exhalation)	34	84	52	51	36	57
Voiced air intake in volume percentage	14	67	35	21	21	45
Unvoiced air intake in volume percentage	86	33	65	79	79	55
Number of respirations	14	3	24	26	36	25

[a] The data were obtained from recording the air flow during the reading of the Rainbow Passage

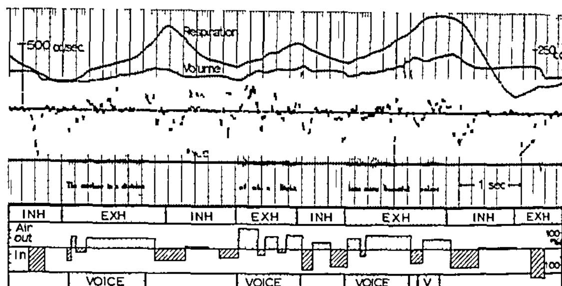


Fig. 2. From top to bottom the traces represent: (1) Respiration. Inhalation is represented by the downward slope, exhalation by the upward curve. (2) Volume of air intake and exsufflation (each heavy graduation consisting of five graduations corresponds to 25 cc). Inward air flow is represented by the downward slope, outward flow by the upward slope. (3) Air flow rate traces above the baseline represent outward flow, below the line inward flow. Each heavy graduation corresponds to 50 cc/sec. (4) Voice. These recordings are schematically shown below by block diagrams. In the second row of the diagram, *flow rate is represented by the height of the block, volume by the area.* The arrow indicates an asynchronous air intake.

An example of the recordings is shown in Fig. 2. A detailed description (Types and Number) of this instrument was given in a previous paper by Isshiki (1964).

Analyses of recordings

In analyzing the complicated sequence of events during esophageal speech, three parameters were taken into consideration as schematically indicated in Fig. 2. These were respiratory movement, direction of air flow and voicing. According to all possible combinations of these three factors, the events during esophageal speech were classified into 8 different categories as shown in Table 1. For each type of different event analyses were made as to the volume and rate of air flow and the duration of the event. The data were summarized for each type of event in order to estimate which type was predominantly utilized for the intake of air and voice production. In interpreting the data for the air flow, special care was taken so that the flow measured by the pneumotachograph did not directly indicate the air flow into the esophagus. Some movement of air sensitized by the pneumotachograph simply resulted from the slight change in the oropharyngeal cavity because of the tongue movement. In general it was noted that if the incoming and outgoing flow of air were limited within the cavity *above the* pseudoglottis, the inward flow of air was immediately followed by the same

The ratio of the synchronous intake of air (Types 3 and 4 in Table 1) to the asynchronous intake of air (Types 1 and 2) was calculated also in terms of *time* for each of the six subjects. The results are shown in Table 2. For example in subject A, 84% of the total period of air intake was used for the asynchronous intake (injection) of air. Roughly speaking, the time ratio of the synchronous intake of air to the asynchronous intake for each speaker is similar to the ratio in terms of the *volume* which was mentioned in the preceding paragraph.

Air intake with or without voicing

If the air is suctioned into the esophagus through the pseudoglottis which is actively opened, the incoming stream of air is usually not accompanied by voice, although if the glottis is closed air intake may accompany the voicing. If the air is actively injected under a positive pressure through the closed glottis, the air flow is more likely to cause vocalization. From these concepts, the air intake was analyzed in relation to vocalization.

The volume ratio of air insufflation with voice (Types 2 and 4 in Table 1) to that without voice (Types 1 and 3) is shown in Table 2 and Fig. 4. A great individual variation in the ratio is noted. Subject A was unique in that a greater volume of air was taken with voicing than without voicing. This finding further indicates that he is an injector. The other subjects insufflated more air without vocalization than with vocalization. It is of great interest to note that this ratio between the voiced insufflation and unvoiced insufflation is quite similar to the ratio between synchronous insufflation and asynchronous insufflation. In other words, it appears that the voiced air intake occurs mostly during the exhalatory phase (voiced injection method) and very seldom during the inhalatory phase (inhalatory phonation).

Comparison of 4 types of air intake

When the two factors of vocalization and the phase relationship with breathing are taken into consideration, the intake of air can be classified into 4 types as shown in Table 1. In order to find the characteristics of each method these four types of air intake were compared with one another in respect to the amount of air intake per trial, the flow rate, the efficiency and the duration of each trial. As shown in Table 3, for all subjects the volume of air insufflated by method 3 (in phase, unvoiced) is greater than that obtained by the other methods. The intake of air by type 4 (synchronous with respiration, voiced), which represents the inhalatory *phonation*, is almost negligible because the number of occurrences and the total volume of air taken in this method are extremely small for all *subjects*. A greater resistance to the incoming air flow is expected when *the air-intake* is accompanied by voice, since during phonation the pseudoglottis is assumed to be closed. This greater resistance of the *pseudoglottis* to the air flow during phonation [illegible] more air can be insufflated without vocaliza-

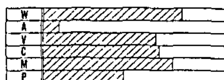


Fig. 3

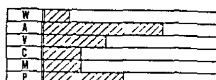


Fig. 4

Fig. 3. Phase relationship between air intake and respiration expressed in volume percentage. The slashed area represents the air intake during inhalation (synchronous intake), the blank area the air intake during exhalation (asynchronous intake).

Fig. 4. Relationship between air intake and voice production. The slashed area represents the voiced air intake, the blank area the voiceless air intake.

P insufflated may be responsible for his poor speech. The efficiency of air intake, however, should be judged not by the total amount of air intake but by the rate of air intake per unit of time (total air intake/total speech time *including the pause between speech*). *The rate of air intake*[1] per unit of time for the subjects ranged from 11.2 cc/sec to 48.6 cc/sec. It was noted that the better the speakers the more efficient the air intake. Speakers C and M, who were ranked 3rd in ability, could insufflate as much air, if not more, than the higher ranked subjects could, but speakers C and M required longer periods of time for this task.

Phase relationship between intake of air and respiration

The inhalation method implies, by definition, that the intake of air is synchronous with the inhalatory movement of the thorax, while in the injection method the intake of air takes place during exhalation as well as inhalation. If the air is insufflated during exhalation or asynchronously with the breathing, it appears that the air was taken in by a variation of the injection method, not the inhalation method. Therefore, an analysis of the phase relationship between the intake of air and respiration is helpful in judging the method of air intake which the esophageal speaker is utilizing.

For each of the six subjects, the percentages of air volume insufflated synchronously with the respiration (Types 3 and 4 in Table 1) during the reading of the Rainbow Passage were calculated and are shown in Table 2 and Fig. 3. It is clear from the table and figure that the means of air intake varies greatly with the individual. Speaker A obtained most (91%) of his air during the exhalatory phase. This asynchrony between air intake and respiration indicates that he is principally an injector. Four subjects, W, V, C, and M insufflated a greater amount of air during inhalation rather than during exhalation. However, all subjects secured some air (above 23% in this investigation) during the exhalatory phase (asynchronous intake of air).

[1] The rate of air intake should be distinguished from the mean flow rate of air which is calculated by dividing the total amount of air intake by the sum of the period of air intake (excluding the rest or expulsion period).

Table 5 *Mean flow rate cc/sec of air intake for four different methods*

Method	Subjekt						Mean
	W	A	V	C	M	P	
Type 1	62	96	83	64	46	57	68
Type 2	50	118	71	45	56	33	62
Type 3	94	58	135	95	73	39	82
Type 4	40	—	123	—	77	30	70

2) and the inhalation method (3) is quite conceivable, because in general the duration of the tongue movement appears shorter than that of the breathing movement

The flow rate for the different types of air intake are shown in Table 5 It is seen that in subject W, V, C, and M who appeared to utilize primarily the inhalation method, the flow rate for method 3 (indicative of inhalation method) is higher than the flow rate for method 1 or 2 (indicative of the injection method) In contrast, the flow rate for method 1 or 2 (injection) was higher than the flow rate for method 3 (inhalation) for speaker A and P, who were regarded as principally using an injection method

Generally during one inhalatory movement, one or two substantial intakes of air occurred The better speakers such as W and V were inclined to perform a greater number of air intakes—sometimes three—during one inhalatory phase, as indicated in Fig 2

The air flow through the oronasal passages during *swallowing* was recorded for all subjects An inward flow of air (usually less than 50 cc) during the initial stage of swallowing was followed by an outward flow of air during the latter stage of swallowing (Fig 5) This phenomenon appears to occur because most of the air movement is limited within the cavity above the pseudoglottis and a very small amount of air may be drawn inefficiently into the esophagus by swallowing

The oronasal air flow during *breathing* indicated that the normal inhalation itself did not introduce any inward movement of air through the nose or mouth in any subjects

Outward flow of air

As indicated in Table 6 most of the outward flow of air from the esophagus or oropharyngeal cavity occurred during the exhalatory phase of respiration (synchrony) regardless of the method of air intake Table 6 also indicates the percentage of the outflow which is accompanied by vocalization Again speaker A a plosive-injector, exhibits a different characteristic in this respect from the other speakers He expels a greater amount of air without voice (unmodulated air flow) than with voice (modulated air flow) In the other speakers, most of the outflow of air expelled during the exhalatory phase was used for voice production Unmodulated air flow

TABLE 3 *Mean volume cc of air intake during one performance using four different methods*

Method	Subject W	A	N	C	M	P	Mean
Type 1	14.4	11.0	10.0	11.8	9.1	7.0	10.55
Type 2	5.9	13.4	8.1	7.8	6.9	5.4	7.92
Type 3	29.9	17.0	17.0	18.5	21.7	9.9	19.0
Type 4	10.0	—	10.8	—	5.7	4.0	7.62

TABLE 4 *Mean duration sec of air intake during one performance using four different methods*

Method	Subject W	A	N	C	M	P	Mean
Type 1	23	12	12	18	20	12	16
Type 2	12	11	11	17	13	16	13
Type 3	32	30	13	20	30	25	25
Type 4	25	—	09	—	07	13	14

tion than with vocalization So far as the amount of air intake is concerned, method 3 (indicative of the inhalatory method) appears most effective, but in respect to the amount of information, method 2 (indicative of the injection method) appears to be more efficient if the voice produced during the air intake is well articulated and intelligible

As indicated in Table 4, one performance of method 3 consumed a longer period of time than did the other methods If we regard method 1 and 2 as the injection methods and method 3 as the inhalation method, then the difference in duration of one action between the injection method (1 and

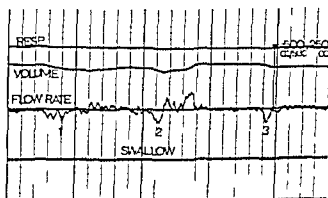


FIG 5 Air flow during swallowing movement The inward flow of air is generally followed by the outward flow

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TABLE 6. *Outward flow of air: relationship with respiration and vocalization, expressed in volume percentage*

	W	A	Y	C	M	P
Synchronous outflow (during exhalation)	91	97	85	69	92	77
Asynchronous outflow (during inhalation)	9	3	15	31	8	23
Voiced outflow	83	44	74	50	81	89
Unvoiced outflow	17	56	26	50	19	11

TABLE 7. *Phonation: relationship with the direction of air flow and respiratory phase, expressed in volume percentage*

	Subject					
Method	W	A	Y	C	M	P
Type 8	84	40	61	65	73	58
Type 2	13	60	24	32	21	36
Type 4 & 6	3	0	15	3	6	6

does not necessarily mean the loss of air, because it may be contributing to the pronunciation of the voiceless consonants. It should be remembered that not all of the outflow without voice (unmodulated air flow) is expelled from the esophagus; some air flow may come from the pharyngeal cavity.

Phonation

When the direction of air flow and the phase relation with respiration are taken into consideration, voice production can be classified into four different types: (1) using the inward flow during exhalation (asynchronic), (2) using the inward flow during inhalation (synchronic), (3) using the outward flow during inhalation (asynchronic), (4) using the outward flow during exhalation (synchronic). These four different kinds of phonations correspond to the types 2, 4, 6, and 8 respectively in the classification in Table 1.

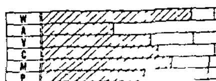


FIG. 6. Three different types of phonation. The slashed area: phonation with outward air flow during exhalation (Type 8); the dotted area: phonation with inward flow of air during exhalation (Type 2); the blank area: phonation during inhalation (Type 4 and 6).

TABLE 8 *The mean flow rates cc/sec for two main types of phonation during speech*

Method	Subject W	A	N	C	M	P	Normal
Type 8	69	97	56	45	66	25	219
Type 2	50	118	71	45	50	33	

Table 7 and Fig 6 show which of these four different methods of voice production is predominantly (in volume and time) employed by each speaker In all of the subjects except A (the plosive injector), the voice was produced predominantly with the outward flow of air during exhalation (Type 8) and to a lesser degree produced with the inward flow of air during the exhalatory phase (Type 2) Speaker A produced voice more by utilizing the inward flow during exhalation than by utilizing the outward flow during exhalation Regardless of the method of air intake used by the subjects the vocal utterances during the inhalatory phase (Types 4 and 6) using either inward or outward air flow were almost negligible The mean flow rates while reading the Rainbow Passage for two main types of vocalization are shown in Table 8 (Types 2 and 8) The mean flow rate during phonation through the use of outward flow of air during exhalation (Type 8) ranged from 25 to 97 cc/sec The mean flow rate for the poorest speaker (P) is substantially lower as compared with those for the other and better speakers The plosive injector A uses a very high rate of air flow for phonation All of the foregoing data were obtained from recording the air flow during the reading of the Rainbow Passage

The mean flow rates for comfortably sustained phonation of the vowel *a* ranged from 27 to 72 cc sec Speaker W continued phonation for a maximum of 4 2 sec The injectors A and P could not prolong the vowel *a* as long as the other speaker could The difference in the flow rates between voiceless consonants and voiced consonants was not as distinct in esophageal speech as in normal speech

DISCUSSION

An analysis of the data revealed that the types of air intake and usage in connection with respiration and vocalization vary greatly with the speakers Furthermore it was suggested that most of the esophageal speakers, here studied used a combination of methods of air intake In order to contrast the differences among those methods a comparison was made between speakers W and A both of whom were superior in esophageal speech and were considered as representing the two different types of esophageal speech

Speaker W took most of the air (76%) *during inhalatory* phase of respira

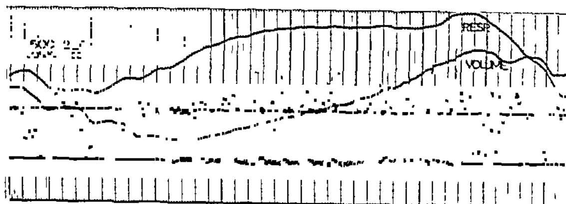


FIG. 7. Maximum repetition (14 times) of the syllable */ba/* with one breath by speaker W. Note that no air intake occurred in connection with the syllable */ba/*.

tion (synchronous intake), while speaker A pumped in almost all the air (91%) during the exhalatory phase (asynchronous intake). A similar tendency was found in time-percentage of air intake: in W, 66% of total time of air intake was used for the synchronous intake (air intake during inhalation), while A used 84% of the total time of air intake for the asynchronous intake. In speaker W, only 14% of the total volume of air intake was accompanied by voice. In speaker A, 67% of the total air intake was voiced. The type and frequency of breathing are also quite different between the two speakers. Speaker W breathed 14 times while reading the 51 words passage, but A breathed only 3 times during the same passage; a normal subject took 6 breaths for the same passage.

In speaker A, the expiration occurred very gradually and slowly. The noise level produced by both speakers at the tracheostoma were too low to attract any attention. Both W and A were excellent in speech performances. For instance, the word per minute indicated 153 word/min for W and 128 for A. The speeches by the two subjects were equally intelligible A's speech, however, was characterized by his overaccentuation of consonant sounds. In the performance of prolonged phonation of the vowel */a/*, speaker W was *much superior to speaker A in that W sustained the vowel /a/ much longer* than did A. Speaker W repeated syllable /ma/ as many times (14) as he did /ba/. This fact suggests that he did not inject air in connection with the plosive consonant (Fig 7).

Since A charged most of the air during the exhalatory phase, it would be safe to conclude that he is an injector. From further analysis of the record of CVC syllable and perceptive judgment of his speech, speaker A appears to be a plosive injector On the other hand, a synchronous intake of air (air intake during inhalation) alone, although highly indicative of the inhaler, is not sufficient to conclude that one is purely an inhaler, because the injection of air can occur theoretically during the inhalatory phase too *The question* is whether or not he is using the tongue to pump air The recording of air flow showed that the normal deep (not so quick as *during speech*)

breathing movement itself without any movement of the tongue did not induce any substantial inflow of air through the oronasal passage

Some portion of air was taken in also during exhalation (asynchronous intake) as indicated by the arrow in Fig 2 The two separate intakes of air during one inhalatory phase as shown in the same figure appeared to correspond to two movements of the tongue Furthermore to an inquiry about his method of air intake speaker W answered that he could not charge air without the movement of the tongue From these findings it was assumed that W was also using the tongue pumping method (injection) From reasoning similar to the above the other subjects were also considered as using both inhalation and injection method although the degree of dominance of one method over the other appeared to vary with the speakers

Earlier work in this area appears to support one particular method and to refute the other methods Moreover some of the articles although they support the various methods give the impression that the speaker has to choose and use only one method the methods appeared incompatible with each other Within the limitation of the present data we feel that many esophageal speakers are unconsciously employing a combination of methods of air intake which we think is recommendable

Naturally insufflation of air into the esophagus by the tongue movement would be greatly facilitated by negative pressure in the esophagus Actually one of the advantages of the inhalation method is a large amount of air intake per trial which can be demonstrated by a sustained phonation of the vowel /a/ As previously mentioned the mean volume of synchronous intake of air (during inhalation) is greater than the volume insufflated during the exhalatory phase (Table 3)

However it should be mentioned that overexertion of the respiratory movement may result in various disadvantages which have been pointed out by many writers These include parasitic noise at the tracheostoma unfavorable effect on the lungs and vascular system fatigue and so on The speakers who repeat deep breathing too frequently during speech with a great tracheal noise should be taught more about the use of the tongue and lips in charging air in and the relaxation of the pseudoglottis as a means of compensation for respiratory overexertion Too much dependence on the inhalation method may sometimes lead to these difficulties mentioned above However these difficulties or disadvantages do not lead to a refutation of the inhalation method at all The important aspect is the balance of the respiratory effort

Some of the earlier authors insisted on the necessity of dissociation among air intake speech and respiration Recent investigators on the other hand presented data favoring synchrony among these factors Robe Moore Andrews & Holinger (1956) supporting the synchrony between oral and pulmonary air movement still mention the need of dissociation among them in some speakers who produce much noise at the tracheostoma The

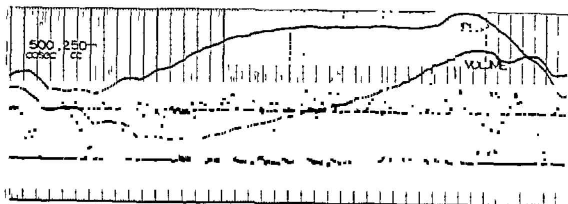


FIG. 7. Maximum repetition (14 times) of the syllable /ba/ with one breath by speaker W. Note that no air intake occurred in connection with the syllable /ba/.

tion (synchronous intake), while speaker A pumped in almost all the air (91%) during the exhalatory phase (asynchronous intake). A similar tendency was found in time-percentage of air intake: in W, 66% of total time of air intake was used for the synchronous intake (air intake during inhalation), while A used 84% of the total time of air intake for the asynchronous intake. In speaker W, only 14% of the total volume of air intake was accompanied by voice. In speaker A, 67% of the total air intake was voiced. The type and frequency of breathing are also quite different between the two speakers. Speaker W breathed 14 times while reading the 51 words passage, but A breathed only 3 times during the same passage; a normal subject took 6 breaths for the same passage.

In speaker A, the expiration occurred very gradually and slowly. The noise level produced by both speakers at the tracheostoma were too low to attract any attention Both W and A were excellent in speech performances. For instance, the word per minute indicated 153 word/min. for W and 128 for A. The speeches by the two subjects were equally intelligible. A's speech, however, was characterized by his overaccentuation of consonant sounds In the performance of prolonged phonation of the vowel /a/, speaker W was much superior to speaker A in that W sustained the vowel /a/ much longer than did A Speaker W repeated syllable /ma/ as many times (14) as he did /ba/ This fact suggests that he did not inject air in connection with the plosive consonant (Fig 7).

Since A charged most of the air during the exhalatory phase, it would be safe to conclude that he is an injector From further analysis of the record of CVC syllable and perceptive judgment of his speech, speaker A appears to be a plosive injector On the other hand, a synchronous intake of air (air intake during inhalation) alone, although highly indicative of the inhaler, is not sufficient to conclude that one is purely an inhaler, because the injection of air can occur theoretically during the inhalatory phase too The question is whether or not he is using the tongue to pump air. The recording of air flow showed that the normal deep (not so quick as during speech)

breathing movement itself, without any movement of the tongue, did not induce any substantial inflow of air through the oronasal passage

Some portion of air was taken in also during exhalation (asynchronous intake) as indicated by the arrow in Fig 2 The two separate intakes of air during one inhalatory phase, as shown in the same figure, appeared to correspond to two movements of the tongue Furthermore, to an inquiry about his method of air intake, speaker W answered that he could not charge air without the movement of the tongue From these findings, it was assumed that W was also using the tongue pumping method (injection) From reasoning similar to the above, the other subjects were also considered as using both inhalation and injection method, although the degree of dominance of one method over the other appeared to vary with the speakers

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suppression of only the respiratory movement does not seem to solve the problem, because this will result in the reduction of the volume of air intake and in the decreased force of air expulsion during phonation. If those noise producing speakers learned to relax the pseudoglottis or the other method of air intake—tongue pumping, the respiratory exertion would naturally be reduced. No further need exists for respiratory overexertion.

The inhalatory phonation (using inflow, during the inhalatory phase) was very rare for all the speakers: the volume percentage of the inhalatory phonation to the total phonation ranged from 0 to 8. The swallowing method was not efficient in air charging. The volume of air swallowed was very small and the swallowing movement could not be repeated rapidly. For the air charge into the esophagus, a laryngectomized patient has to learn correct movements of the tongue and the lips which have not been used prior to laryngectomy.

Some movement of the tongue and the other articulatory organs which are used in normal speech before laryngectomy are similar to the movements necessary for air insufflation, and therefore can be utilized as cues to the new movements to be learned. These are, for instance, pronunciation of the plosive consonants and swallowing. Many investigators (van Gilse 1949, van den Berg, Moolenaar-Bijl & Damsté 1958, Schlosshauer & Möckel, 1958) have already described the initial phase of swallowing as resembling the action of the tongue required for air insufflation. It should be emphasized to the patient that the total action of swallowing is not appropriate for an intake but only the initial stage need be used.

A general discussion on the coordination of air intake with respiration would not be realistic, without a consideration of the method of air intake that the speaker is utilizing. In an inhaler, more synchrony between air intake and respiration is noted than in an injector. Actually, there would be no simple answer to this problem: synchrony or asynchrony. Most speakers employ both synchronic and asynchronic intake of air in various degrees depending on the method of air intake. In this study, the majority of speakers (inhalation and injection) charged more air synchronously than asynchronously.

The phase relationship between speech and respiration also depends on the method of air intake used. Most (85–100% in volume) of the phonations were made during the exhalatory phase using either inflow or outflow (Type 2 and 8 in Table 1). Excluding the plosive injector A, the present speakers produced voice mainly by utilizing the outward flow (Type 8).

As exemplified by the two superior esophageal speakers who were utilizing different methods, no one single method appeared best suited for any speaker. It was shown that a pneumotachographic technique for measuring flow rate presents a useful means of analyzing the sequence of events during esophageal speech. Further research through this technique alone or in combination with other methods is needed in this field not only for superior speakers such as those studied here but also for less able speakers.

ACKNOWLEDGMENT

The authors express their appreciation to Hans von Leden, M.D., and Elvira Werner Kukuk, M.D. for their cooperation in this study. The subjects were nominated by Morton Cooper, Ph.D., and Robert Harrington, Ph.D., both of whom are experienced teachers of esophageal speech.

ZUSAMMENFASSUNG

Der Grad und Umfang des oronasalen Luftflusses, also respiratorische Bewegungen und Stimmsignale, wurden gleichzeitig an sechs Oesophagus-Sprechern während diejenigen sprachen, schluckten und atmeten, registriert. Eine Analyse der Befunde hat Folgendes ergeben:

1) Die Methode der Luftaufnahme zeigte grosse individuelle Unterschiede. Ein Plosive-Injektor belastete sich mit der meisten (91%) ihm zur Verfügung stehen den Luft während der Ausatmung, dagegen sogen vier Sprecher, welche die Inhalations- und Injektionsmethode benutzten, stimmlos mehr Luft ein während der Inhalation als bei der Ausatmung.

2) Alle Testpersonen mit der Ausnahme des Plosive-Injektors erzeugten ihre Stimme vorwiegend mit Fluss der Luft nach aussen während der Ausatmung.

3) Der Luftfluss-Mittelwert für bequem aufrechterhaltenem Vokal /a/ lag zwischen 27 and 72 cc/sec.

4) Die Inhalationsphonation war für alle Sprecher nicht beachtenswert. Der Akt des Schluckens ist nicht empfehlenswert für Lufteinnahme.

5) Einige klinische Zusammenhänge der experimentellen Resultate und der pneumotachographischen Methoden wurden diskutiert.

REFERENCES

BERG, J. VAN DEN, MOOLENAAR-BIJL, A. J. and DAMSTE, P. H., 1958. Oesophageal speech. *Folia Phoniat.* (Basel) *10*, 65.

BERG, J. VAN DEN and MOOLENAAR-BIJL, A. J., 1959. Crico-pharyngeal sphincter, pitch, intensity and fluency in oesophageal speech. *Pract. Ot-rhinolaryng.* (Basel) *21*, 298.

BRIGHTON, G. R., and BOONE, W. H. 1937. Roentgenographic demonstration of method of speech in case of complete laryngectomy. *Amer. J. Roentgenol. 38*, 571.

BERGER, H. and KAISER, L., 1925. Speech without a larynx. *Acta Otolaryng.* (Stockh.) *8*, 90.

CURRY, E. T., and SNIDECOR, J. C. 1961. Physical measurement and pitch perception in esophageal speech. *Laryngoscope 71*, 3.

DAMSTE, P. H., 1958. *Oesophageal speech after laryngectomy.* Groningen.

DIEDRICH, W. M. and YOUNGSTROM, K., 1962. *An investigation of speech after laryngectomy.* Office of Vocational Rehabilitation Summary Report Project No. 337.

FROESCHELS, E. 1951. Therapy of the alaryngeal voice following laryngectomy: a contribution. *Arch. Otolaryng.* (Chic.) *53*, 77.

GILSE, P. H. G. VAN, 1949. Another method of speech without larynx. *Acta Otolaryng.* (Stockh.) Suppl. *78*, 109.

GUTZMANN, H. 1909. Stimme und Sprache ohne Kehlkopf. *Z. Laryng. Rhinol. Otol.*, *1*, 221.

HODSON, C. J. and OSWALD, M. V. O., 1958. *Speech Recovery after Total Laryngectomy.* E. and S. Livingstone Ltd., Edinburgh and London.

Howie, T O 1947 Rehabilitation of the patient after laryngectomy *Occup Ther* 26 372

Isshiki N., 1964 Regulatory mechanism of voice intensity variation *J Speech Hearing Res* 7, 17

Isshiki N and von Leden, H Hoarseness Aerodynamic studies *Arch Otolaryng* (Chic) (in press)

Kaiser L 1926 Examen phonetique d un sujet privé de larynx *Arch Néerl Physiol* 10 468

Moolenaar-Bijl A J 1953 Connection between consonant articulation and the intake of air in oesophageal speech *Folia Phoniat* (Basel), 5 212

Robe E Y Moore P Andrews A H Jr and Holinger P H 1956 A study of the role of certain factors in the development of speech after laryngectomy 3 Coordination of speech with respiration *Laryngoscope* 66 481

Schilling R 1927 Über die Pharynx und Oesophagusstimme *Z Hals Nas Ohrenheilk* 9 893

Schlosshauer B and Mockel, G., 1958 Auswertung der Röntgenfilmnahmen von Speiseröhrensprechern *Folia Phoniat* (Basel), 10 154

Seeman M., 1958 Zur Pathologie der Ösophagusstimme *Folia Phoniat* (Basel) 10 44

Snidecor J C 1951 Pitch and duration characteristics of superior female speakers during oral reading *J Speech Hearing Dis* 16 44

— 1962 *Speech Rehabilitation of the Laryngectomized* C C Thomas Springfield Illinois 1962

Stetson R H 1937 Esophageal speech for any laryngectomized patient *Arch Otolaryng* (Chic) 26 132

Sugano M., 1962 Study on oesophageal speech *J Jap Bronchooesophag Soc* 13 135

Wepman J M MacGahan J A Rickard J C, and Shelton N W., 1953 Progressive nature of esophageal speech development and its objective measurement *J Speech Hearing Dis* 18 247

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MORPHOLOGICAL STUDY OF THE LARYNGEAL MUSCLES IN MAN

Insertions and Courses of the Muscle Fibres, Motor End Plates and Proprioceptors

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Koelle and Friedenwald s test for acetylcholinesterase has been used in a study on the following laryngeal muscles in man vocalis cricothyroid lateral crico arytenoid and posterior crico arytenoid Serial sections were made with the freezing microtome and a number of muscles were submitted to microdissection Multi motor end plate fibres were found in all four muscles studied (70 to 80 per cent in the vocalis muscle about 50 per cent in the cricothyroid and lateral crico arytenoid muscles and about 5 per cent in the posterior crico arytenoid muscle) None of the fibres of the vocalis muscle was found to be inserted into the vocal ligament Only in the vocalis muscle was it possible to demonstrate typical muscle spindles whereas in all four muscles studied spiral nerve endings were observed

A careful study of the literature on the microscopic anatomy of the larynx has brought to our attention three aspects of the subject which although extensively investigated by a large number of workers still await definitive elucidation

(1) *Insertions and Courses of the Fibres of the Vocalis Muscle*

There are two main currents of thought on this point Supporters of the first claim that there exist not only thyro arytenoid fibres but also fibres which are inserted into the vocal ligament Such are Lauth (1837), Ludwig (1858) Ruhlmann (1874) Grutzner (1879), Shattock (1881), Jacobsohn (1887) Giacomini (1892) Bertelli (1922), Rouviere (1924) Simonetta (192) Schimert (1934) Tavani (1935) Roncallo (1939) Brash (1941) Pressman (1942) Goertller (1948 1951) Berendes (1950) Terracol & Guilbert (1953) Motta (1954) Behringer (1955) Amati & Pirro (1955) Seiter (1956) Terracol Guerrier & Camps (1956), Boccuzzi (1961), Marco & Lopez de la Torre (1962) Galletti (1962) and Zenker (1963)

Supporters of the second deny the existence of fibres inserted into the vocal ligament accepting only that of thyro-arytenoid fibres Such are Luschka (1871) Henle (1873) Sappey (1877) Kanthack (1889) Gegen

baur (1895), Merkel (1901), Moller (1901), Raubel (1902), Lasagna (1914), Orlandini (1916), Testut (1923), Elze (1925), Negus (1929), Favaro (1935), Nemai (1937), Fazzari (1948), Chiarugi (1948), Wustrow (1952, 1956), Mayet (1955 *a*, *b*), van den Berg & Moll (1955), Vosteen (1957), Schlossauer & Vosteen (1957, 1958), Ruedi (1959), Manjome (1959), and Sonesson (1960)

There are also writers who maintain that, apart from fibres inserted into the vocal ligament, there exist fibres which are inserted into the crico-vocal membrane This is the view of Ruhlmann (1874), Goerttler (1918 1951), Behringer (1955). Yet others (Mayet, 1955 *a*, *b*, van den Berg & Moll, 1955, Schlossauer & Vosteen, 1957, 1958, and Sonesson, 1960), although denying the existence of fibres inserted into the vocal ligament, do admit that some fibres are inserted into the cricovocal membrane

(2) *Arrangement and Features of the Motor End-Plates of the Vocalis Muscle*

It is known that in mammalian skeletal muscle the motor end-plates one for each fibre, are situated approximately mid-way between the two points of insertion of each muscle fibre In a muscle composed of fibres of equal length the motor end-plates are thus arranged in a row to form the "motor region" (Coërs, 1953, 1955, 1959, Häggquist, 1956, Desmedt, 1958, and Schwarzacher, 1959) Exceptions are found in the human orbicularis muscle of the eyelid (Desmedt, 1958) and the lateral rectus muscle of the orbit (Kupfer, 1960), which possess several motor end-plates arranged on a single muscle fibre This arrangement was also observed in predominantly tonic muscles of Batrachia (Kuffler & Vaughan Williams, 1953) and Birds (Ginsborg 1959, Ginsborg & Mackay, 1961)

Recently "multi-motor end-plate" muscle fibres have been postulated for the human vocalis muscle (Piquet, Hoffmann & Husson, 1957, Piquet & Barrets, 1960, Zenker, 1963) On the strength of findings obtained from studies employing the silver impregnation method, Rudolph (1960, 1961, 1962) advances the view that in the human vocalis muscle there is one multi-motor end-plate fibre for every five single-motor end-plate fibres

On the other hand that such fibres exist in the human vocalis muscle is denied by Sonesson (1960), who used Koelle & Friedenwald's method (1949) and by Konig & van Leden (1961 *a b*), who used the silver impregnation method

No mention is made of the problem in the reports of Gerebtzoff & Lepage (1959) or Christensen (1959), who studied the vocalis muscle by histochemical methods for acetylcholinesterase

(3) *Existence of Proprioceptors in the Laryngeal Muscles*

A number of investigators using different histological or histochemical techniques, have demonstrated in the human vocalis muscle the presence

of receptors thought to be muscle spindles (Laskov 1955 Paulsen 1958 Zwirnen 1958 Gerebtzoff & Lepage 1959 Pennetta 1959 von Lanz & Mayet, 1959 Konig 1961 Konig & van Leden 1961 *a b* Goerttler, 1961 Lucas Keene 1961 Terracol & Ardouin 1964) On the strength of electroneurographic findings Molinari (1962 *a b*) and Bianconi & Molinari (1962) postulate the existence of muscle spindles in the cat vocalis muscle Other writers firmly deny their existence in the human vocalis muscle (Chimbaris 1910 Mundnich 1937 Fernand & Young 1951 Murray 1957 and Galletti 1962)

Muscle spindles have also been reported in the posterior crico arytenoid and cricothyroid muscles (Paulsen 1958) in the lateral crico arytenoid muscle (Winckler 1957) and in the transverse arytenoid muscle (Goerttler 1961)

Finally another group of investigators has reported proprioceptor endings different from muscle spindles in the vocalis muscle Von Lanz & Mayet (1959) and Konig & van Leden (1961 *a b*) describe proprioceptor endings which they define as Endkorpes Rudolph (1961) has described nerve fibres which appear to be wound around a single muscle fibre for part of its course he has termed these spiral nerve endings Goerttler (1961) reported the finding of Myofibrillares Endorganes proprioceptor endings smaller than the spindles

In view of the conflicting or widely divergent views which have been advanced on these three problems it was thought worth while attempting to shed light on the areas of obscurity which have so far defied satisfactory or at least universally accepted explanation

MATERIALS AND METHODS

The present investigation was conducted on the following laryngeal muscles vocalis muscle posterior crico arytenoid muscle lateral crico arytenoid muscle and cricothyroid muscle

All four muscles were obtained from total laryngectomy specimens Twenty five larynges from males between 48 and 65 years of age were chosen Naturally muscles affected by neoplastic disease were avoided

The operative specimens were fixed *in toto* for three hours in 10 per cent neutral formalin The muscles were then carefully dissected care being taken to preserve their insertions intact For this purpose the perichondrium was detached from the cartilage at the point of insertion of the muscle Since the vocalis muscle is laterally poorly demarcated from the lateral thyro arytenoid muscle only the medial two thirds of the muscular mass contained in the vocal cord were removed for study

Longitudinal serial sections 50 µ thick of 10 vocalis 10 posterior crico arytenoid 10 lateral crico arytenoid and 10 cricothyroid muscles were obtained from the freezing microtome The sections were submitted to Koelle

and Friedenwald's test for acetylcholinesterase (1949) (*K. and F. AChE test*), as modified by Holmstedt (1957 *a, b*).

Ten vocalis, 10 posterior crico-arytenoid, 10 lateral crico-arytenoid and 10 cricothyroid muscles were submitted *in toto* to the K. and F. AChE test, followed by microdissection of the individual muscle fibres.

Three vocalis, 3 posterior crico-arytenoid, 3 lateral crico-arytenoid and 3 cricothyroid muscles were studied by means of Azan-Mallory staining. Serial reconstructions were made with sections perpendicular to the major axis.

For purposes of comparison, the K. and F. AChE test was also used to study another human striated muscle, the pectoralis major, obtained from a radical mastectomy.

Each of the sections was studied *in order to determine the morphological* features and general arrangement of the motor end-plates, identify the zone of insertion of the fibres of each individual muscle, and verify the existence of the proprioceptors. A search for proprioceptor cells was also made in the sections subjected to Azan-Mallory staining.

Finally, the arrangement of the motor end-plates was studied in the individual fibres isolated by microdissection.

RESULTS

In attempting to solve the problem of whether or not vocalis muscle fibres are inserted into the vocal ligament, account was taken of the finding of Couteaux (1953), *Gerebtzoff* (1954), *Gerebtzoff & Ueten* (1954), Coërs (1959), and Sonesson (1960) that at the point of insertion of each muscle fibre there is an acetylcholinesterase-positive zone, termed by Gerebtzoff (1954) "manchon enzymatique" and by Coërs (1959) "cholinesterasic cuff".

No "cholinesterasic cuffs" were found in the vocal ligament in any of the vocalis muscle sections studied. They were, however, constantly found at the points of insertion into the thyroid cartilage and arytenoid cartilage (Plate A, Fig. 1). A number of "cholinesterasic cuffs" were constantly found at the cricovocal membrane.

The impression gained, therefore, was that no *muscle fibres are inserted* into the vocal ligament, so that fibres coursing towards this ligament *merely pass it longitudinally without attaching to it*. On the other hand, there do seem to be a few vocalis muscle fibres which are inserted into the cricovocal membrane.

"Cholinesterasic cuffs" were also found at the points of insertion on the respective cartilages of the lateral crico-arytenoid and cricothyroid muscles. There is good reason to believe that all the fibres of these two muscles, as well as of the vocalis muscle, course directly and continuously between the cartilages of insertion. They can therefore be regarded as *type I*, according to Coërs' classification (1959).

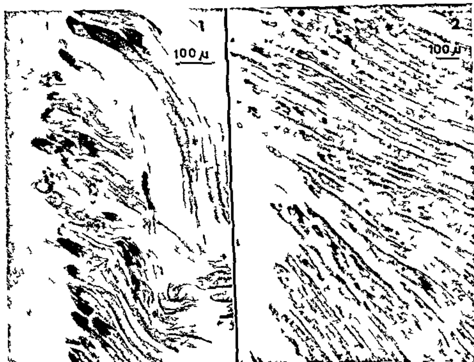


PLATE A

Fig. 1. *Vocalis muscle:* insertion of the muscle fibres into the thyroid cartilage. The "cholinesteratic cuffs" are arranged more or less in a single row.
Fig. 2. *Posterior crico-arytenoid muscle:* insertion of the muscle fibres into connective tissue shoots within the fibres. The "cholinesteratic cuffs" are seen at different levels.

(Koelle and Friedenwald's acetylcholinesterase test.)

In the posterior crico-arytenoid muscle the situation is diffferent. Apart from fibres coursing continuously from the cricoid cartilage to the arytenoid cartilage, there are also others which terminate at connective tissue shoots situated within the muscle tissue. Cholinesteratic cuffs were in fact constantly found in the vicinity of these shoots (Plate A, Fig. 2). The posterior crico-arytenoid muscle thus belongs to type III according to Coers classification (1959).

As regards the arrangement and morphological features of the motor end plates in human laryngeal muscles, the use of the K. and F. AChE test to study this problem was prompted by Rudolph's finding (1962) that not all the motor end plates of a muscle are disclosed by the silver impregnation method. This, he points out, can only be achieved with the AChE reaction, which, unlike the silver impregnation method, depicts with great accuracy the subneural apparatus (Couteaux 1952, Couteaux & Taxi 1952). It was thus decided to study the arrangement of motor end plates in human laryngeal muscles by the AChE reaction method.

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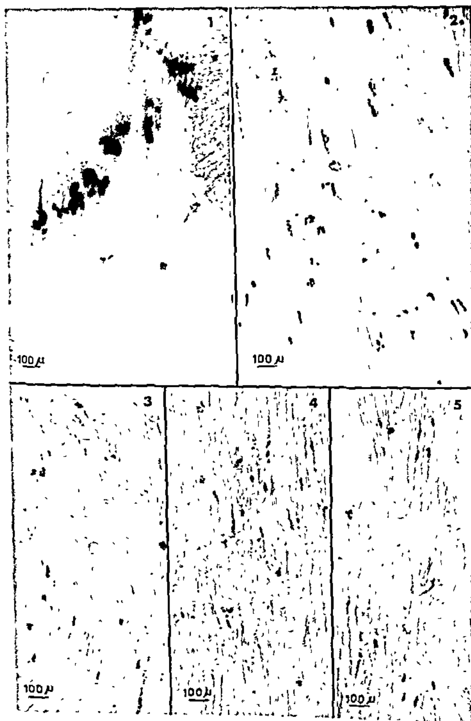


PLATE II

A preliminary low power microscopic examination of the serial sections obtained from the freezing microtome and submitted to the K and F AChE test disclosed that the motor end-plates in the vocalis muscle are not arranged in a single row in the middle of the muscle but are scattered over an area occupying about two-thirds of the entire muscular mass (Plate B Figs 1 and 2) This is the opposite of what is found in striated muscles of man made up of fibres of equal length coursing uninterruptedly from one end of the muscle to the other The same findings were obtained in the cricothyroid and lateral crico-arytenoid muscles (Plate B, Figs 3 and 4)

An examination of the arrangement of the "cholinesteratic cuffs" showed that these three muscles are made up of fibres coursing continuously from one head of insertion to the other. This suggested that there might be a relationship between the arrangement of the motor end-plates and the existence of more than one motor end-plate on a single muscle fibre

In order to investigate the validity of this hypothesis, we examined the fibres of these muscles, isolated by microdissection, under medium and high power Numerous fibres of the three muscles were observed to contain several motor end-plates

In the vocalis muscle there were fibres containing between 1 and 5 motor end-plates (Plate C, Figs 1–7), whereas in the lateral crico-arytenoid and cricothyroid muscles no fibres were found to contain more than three motor end-plates

By counting the motor end-plates on 100 fibres of each of the 10 vocalis muscles submitted to microdissection, it was found that between 70 and 80 per cent of the vocalis muscle fibres contain more than one motor end plate In the lateral crico-arytenoid and cricothyroid muscles this figure falls to around 50 per cent

Two-thirds of the multi-motor end-plate fibres making up the vocalis muscle were found to contain two motor end-plates the remaining muscle fibres of multiple innervation had for the most part three and in a few instances four or five motor end-plates

It was also noted that the two motor end-plates in a single muscle fibre were not always the same distance apart In some fibres they were separated by a distance of under 50 μ and in others by over 1000 μ This variable spacing was also found in the fibres containing 3, 4 or 5 motor end-plates

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PLATE B

Fig 1 Arrangement of motor end plates in the pectoralis major muscle
Fig 2 Arrangement of motor end plates in the vocalis muscle
Fig 3 Arrangement of motor end plates in the cricothyroid muscle
Fig 4 Arrangement of motor end plates in the lateral crico arytenoid muscle
Fig 5 Arrangement of motor end plates in the posterior crico arytenoid muscle

(Koelle and Friedenwald's acetylcholinesterase test

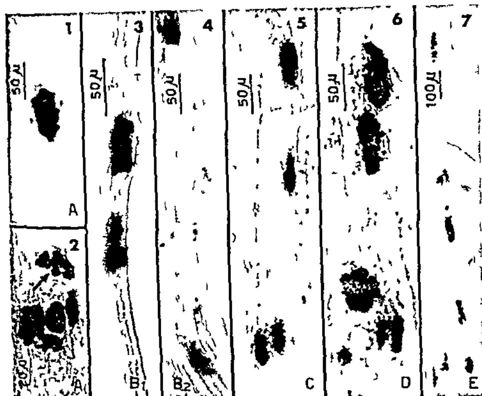


PLATE C

Vocalis muscle

Fig 1 Muscle fibre with a single motor end plate (type A)

Fig 2 Type A muscle fibre containing a motor end plate with an accessory plate denoted by arrow

Fig 3 Muscle fibre with 2 motor end plates less than 50 μ apart (type B₁)

Fig 4 Muscle fibre with 2 motor end plates over 50 μ apart (type B₂)

Fig 5 Muscle fibre with 3 motor end plates (type C)

Fig 6 Muscle fibre with 4 motor end plates (type D)

Fig 7 Muscle fibre with 5 motor end plates (type E)

(Koelle and Friedenwald's acetylcholinesterase test)

In the cricothyroid muscle and lateral crico arytenoid muscle by far the majority of multi motor end plate fibres contained 2 motor end plates whereas only very few had 3 motor end plates In these muscles no fibres with 4 or 5 motor end plates were found As regards the spacing of the motor end plates in these multi motor end plate fibres the findings were the same as for the vocalis muscle

Table 1 shows the break down by type of muscle fibre, of the motor end plate count Type A comprises fibres with a single motor end plate … plates less than 50 μ apart type B, those

TABLE 1

Muscle No	Muscle fibre type A	B_1	B_2	C	D	E
Vocalis muscle						
1	22	26	30	12	3	1
2	29	19	32	16	4	—
3	25	20	33	15	6	1
4	25	23	33	14	5	—
5	21	25	37	15	2	—
6	23	28	32	15	2	—
7	24	21	31	18	2	1
8	26	21	31	18	4	—
9	24	23	35	13	5	—
10	25	25	33	14	2	1
Crico-thyroid muscle						
1	51	18	29	2	—	—
2	48	20	28	4	—	—
3	57	16	22	5	—	—
4	59	18	22	1	—	—
5	56	19	23	2	—	—
6	55	21	21	2	—	—
7	52	23	22	3	—	—
8	52	22	24	2	—	—
9	53	21	19	4	—	—
10	55	22	21	2	—	—
Lateral crico-arytenoid muscle						
1	44	20	31	5	—	—
2	45	22	31	2	—	—
3	44	20	29	7	—	—
4	48	19	27	6	—	—
5	49	23	26	2	—	
6	48	24	23	5	—	
7	47	18	30	5		
8	42	22	32	4		
9	41	25	31	3		
10	45	20	30	5		
Posterior crico-arytenoid muscle						
1	90	5	4	1		
2	95	2	1	2		
3	92	4	3	1		
4	98	1		1		
5	96	1	2	1		
6	97	1		2		
7	97	2	1			
8	95	3	–			
9	93	1	1			
10	94	2	3	1		

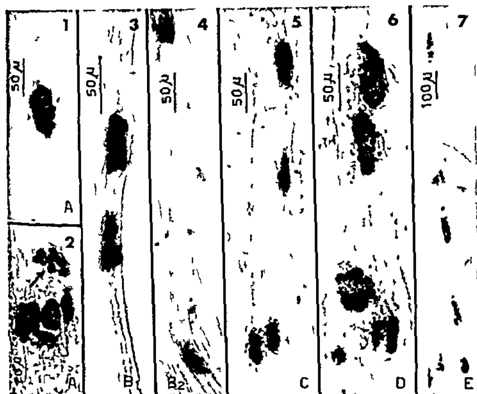


PLATE C

Vocalis muscle

Fig 1 Muscle fibre with a single motor end plate (type A)
Fig 2 Type A muscle fibre containing a motor end plate with an accessory plate (denoted by arrow
Fig 3 Muscle fibre with 2 motor end plates less than 60 µ apart (type B1)
Fig 4 Muscle fibre with 2 motor end plates over 50 µ apart (type B2)
Fig 5 Muscle fibre with 3 motor end plates (type C)
Fig 6 Muscle fibre with 4 motor end plates (type D)
Fig [illegible] Muscle fibre with 5 motor end plates (type E)

(Koelle and Friedenwald's acetylcholinesterase test)

In the crico-thyroid muscle and lateral crico-arytenoid muscle by far the majority of multi-motor end-plate fibres contained 2 motor end plates whereas only very few had 3 motor end plates. In these muscles no fibres with 4 or 5 motor end plates were found. As regards the spacing of the motor end plates in these multi-motor end-plate fibres the findings were the same as for the vocalis muscle.

Table [illegible] shows the break-down by type of muscle fibre of the motor end-plate count. Type A comprises fibres with a single motor end plate, type B1 those with 2 motor end plates less than 50 µ apart, type B2 those

with 2 motor end-plates over 50 μ apart, type C those with 3 motor end-plates, type D those with 4 motor end-plates, and type E those with 5 motor end-plates

A special word should be said about the posterior crico-arytenoid muscle Under low power, the sections obtained from the freezing microtome again exhibited a scattered motor end-plate arrangement (Plate B, Fig 5) As we have already mentioned, however, this muscle is made up not only of fibres which course continuously *from the cricoid to the arytenoid cartilage* but also of fibres terminating at the connective tissue shoots found within the muscle tissue This characteristic make-up of the posterior crico-arytenoid muscle could alone account for the scattered arrangement of the motor end-plates without any need to invoke the existence of multi-motor end-plate fibres

Medium and high power examination of the muscle fibres isolated by microdissection showed that about 95 per cent contain a single motor end-plate Hence, this muscle also contains a few fibres (5 per cent) with 2 or at most 3 motor end-plates

Finally, a detailed study was made of the morphological features of the individual motor end-plates in the different muscles examined Evidence of both simple and compound motor end-plates was obtained (Plate D, Figs 1–5)

Simple motor end-plates were of varying sizes in some, the major diameter was over 150 μ Each had a single subneural apparatus and showed no constrictions nor breaks (Plate D, Figs 1 and 2)

Compound motor end-plates presented a bilobate, trilobate or tetralobate appearance owing to constrictions or breaks in the subneural apparatus (*Plate D, Figs 3, 4 and 5*)

Each motor end-plate whether simple or compound displayed a characteristic acetylcholinesterase arrangement which gave to the subneural apparatus a typical grape-like configuration (Plate D, Figs 1 and 2)

A small zone exhibiting positivity to the K and F AChE test was noted near a few motor end-plates (Plate C Fig 2) This zone was also noted by, among others Kupfer (1960), in the lateral rectus muscle of the orbit He regards it as an accessory end-plate corresponding to the termination of either a sympathetic or a parasympathetic fibre

Both simple and compound motor end-plates could be found in either single-motor end-plate fibres or multi-motor end-plate fibres of the four muscles studied in the present investigation, and no clear-cut relationship could be ascertained between morphological type of end-plate and number of motor end-plates in any individual muscle *fibre*

A number of structures in the four laryngeal muscles studied in the present investigation exhibited positivity to the K and F AChE test These are thought to be muscle receptors Coers (1959) reports the successful application of the K and F test to the study of muscle proprioceptors In-

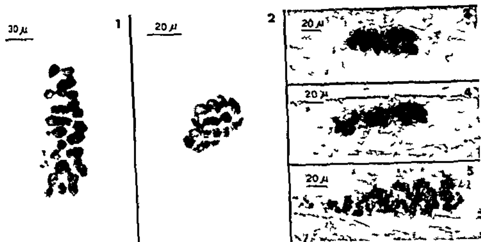


PLATE D

Vocalis muscle

Fig 1 Simple motor end plate over 50 μ long
Fig 2 Simple motor end plate less than 50 μ long
Fig 3 Compound bilobate motor end plate
Fig 4 Compound trilobate motor end plate
Fig 5 Compound tetralobate motor end plate

(Koelle and Friedenwald's acetylcholinesterase test)

deed it is Coers findings (1959) in other human striated muscles which form the basis of the present interpretation of our observations

Firstly the vocalis muscle was found to contain certain elongated structures about the same length as the muscle and made up of a variable number of fibres around and within which was seen a close knit mesh of fibres and nerve endings These were either elongated or ramifying and displayed positivity to the K and F AChE test (Plate E Figs 1 and 2) Between two and five of these structures were found in each vocalis muscle in the part adjacent to the vocal ligament At certain points in their course they seemed isolated within this ligament In a few instances they were found within the vocalis muscle tissue itself

Histological control examination of the vocalis muscle using Azan-Mallory's stain revealed in approximately the same sites structures identifiable as muscle spindles by the presence of a well defined connective tissue capsule and a perifascicular space and by the appearances of the muscle fibres they contained (Plate E Figs 4 and 5)

Structures such as those described above could not be found in the other three laryngeal muscles studied In all four laryngeal muscles nerve endings were found These consisted of a nerve fibre which was strongly positive to the K and F AChE test and was coiled in a spiral around one and sometimes two muscle fibres (Plate F Fig 6) They were far more

with 2 motor end-plates over 50 μ apart, type C those with 3 motor end-plates, type D those with 4 motor end-plates, and type E those with 5 motor end-plates

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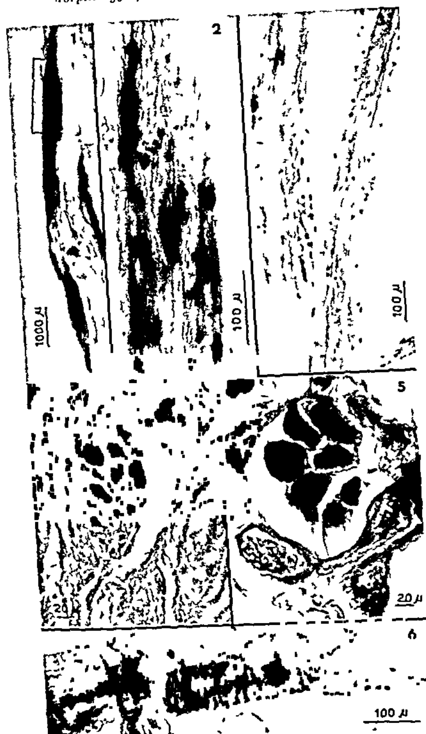
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1
2
1000 μ
100 μ
100 μ
5
20 μ
20
6
100 μ

numerous than the muscle spindles and were noted in greater numbers in "spindle-less" laryngeal muscles. In some cases the vocalis muscle contained about ten of these structures, although in the other muscles between 15 and 25 were counted.

The muscle fibres with coiled "spirals" were the same size as the other fibres of the muscle, as is not the case with muscle spindles.

The "spirals" were not coiled around the whole length of the fibre but only for 150 to 200 μ of its length. In the vocalis muscle they are mainly found just beneath the vocal ligament, whereas in the other three muscles they are scattered over a wider area.

By reason of their morphological features, site and size, the above structures can be considered identical to the proprioceptor endings demonstrated by Rudolph (1961), using the silver impregnation method, in the vocalis muscle alone and termed by him "spiral nerve endings".

Finally, all the muscles studied were found to contain fibres presenting on their surfaces widely spaced and regular, almost symmetrical zones of positivity to the K. and F. AChE test (Plate E, Fig. 3). Gerebtzoff & Lepage (1959), using the same K. and F. AChE test, also observed these structures which they interpreted as muscle spindles. In view of the findings of the present investigation, we are unable to share this interpretation. Indeed, we have described structures quite different from those in question but which did exhibit the typical features of muscle spindles. There is, we feel, insufficient evidence on which to assess the significance of these structures.

CONCLUSIONS

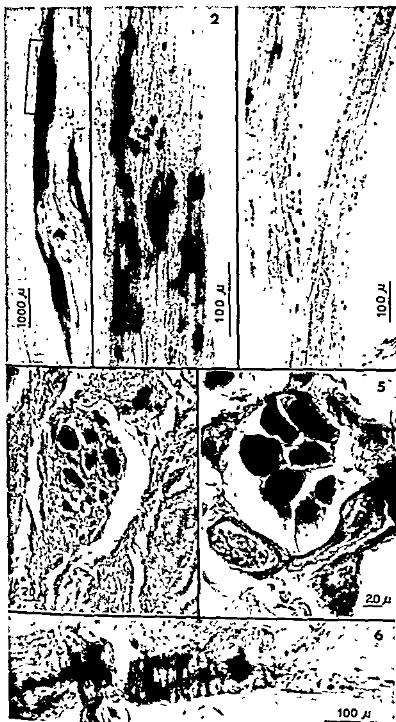
From the foregoing studies on the vocalis muscle, cricothyroid muscle, posterior crico-arytenoid muscle and lateral crico-arytenoid muscle of man, the following conclusions are warranted.

1. "Cholinesteratic cuffs" are found in the fibres of the vocalis muscle only at their insertions into the thyroid cartilage and arytenoid cartilage. This indicates that these fibres course continuously and directly from one cartilage of insertion to the other without attaching to the vocal ligament.

PLATE I

Fig. 1. Muscle spindle within the vocal ligament.
Fig. 2. High power detail of preceding figure.
Fig. 3. Vocalis muscle fibre with a large number of small nerve endings displaying positivity to the reaction for acetylcholinesterase.
Fig. 4. Cross section of muscle spindle in the vocal ligament.
Fig. 5. Muscle spindle within the vocalis muscle.
Fig. 6. "Spiral nerve ending" around a vocalis muscle fibre.

(Figs. 1, 2, 3 and 6: Koelle and Friedenwald's acetylcholinesterase test. Figs. 4 and 5: Azan Mallory stain.)


1
2
3
1000 µ
100 µ
100 µ
4
5
20 µ
20 µ
6
100 µ

On the other hand, a number of fibres are inserted into the cricovocal membrane.

2. The lateral crico-arytenoid and cricothyroid muscles *are also made up* of fibres which course continuously from one cartilage of insertion to the other.

3. The posterior crico-arytenoid muscle, however, is made up not only of fibres coursing continuously between the two cartilages of insertion but also of fibres which terminate at connective tissue shoots ramifying at different levels into the muscular tissue.

4. In the four muscles studied, fibres were found possessing more than *one motor end-plate. Fibres with 2, 3, 4 and even 5* motor end-plates were found in the vocalis muscle, whereas in the other three muscles there were no fibres containing more than three motor end-plates. About 70 to 80 per cent of the fibres making up the vocalis muscle are of this "multi-motor end-plate" type. In the cricothyroid and lateral crico-arytenoid muscles they account for about 50 per cent of the total fibres in the muscle and in the posterior crico-arytenoid muscle, only 5 per cent.

5. In the four laryngeal muscles studied the motor end-plates are not arranged in a single row mid-way between the two insertions as in the other human skeletal muscles but are scattered over an area occupying about two-thirds of the length of the muscle. In the vocalis muscle, cricothyroid muscle and lateral crico-arytenoid muscle, this finding is directly related to the fact that in these muscles there are multi-motor end-plate fibres. The *posterior crico-arytenoid muscle, on the other hand,* has very few multi-motor end-plate fibres and in this case the above finding is related to the different lengths of the fibres terminating at connective shoots situated at different levels in the muscle tissue.

6. Typical muscle spindles were only found in the vocalis muscle.

7. *Proprioceptor* "spiral nerve endings" were *found in all four muscles* studied.

RESUME

Au moyen de la reaction de Koelle et Friedenwald pour l'acetylcholinesterase un examen des muscles laryngiens de l'homme a ete effectue (couche *interne du* muscle thyro-arytenoidien, muscle crico-thyroidien, muscle crico-arytenoidien lateral, muscle crico-arytenoidien posterieur) sur des coupes seriees obtenues au microtome a congelation et sur des preparations pour microdissection. *Dans tous* les muscles examines, des fibres a innervation multiple furent trouvees (70-80% dans la couche interne du muscle thyro-arytenoidien, 50% environ dans le muscle crico-thyroidien et dans le muscle crico-arytenoidien lateral, 5% environ dans le muscle crico-arytenoidien posterieur). Aucune fibre de la couche interne du muscle thyro-arytenoidien s'insere sur les ligaments vocales. Seule dans la couche interne du muscle thyro-arytenoidien existent des fuseaux neuromusculaires *typi*ques, tandis que dans tous les muscles examines existent des expansions proprioceptives du type "spiral nerve ending".

ZUSAMMENFASSUNG

Eine Untersuchung der Kehlkopfmuskeln des Menschen (M vocalis, M cricotireoideus M crico aritenoideus lateralis, M crico aritenoideus dorsalis) mittels Koelles und Friedenwalds Acetylcholinesterase Reaktion wurde durchgeführt Serienschnitte wurden mit dem Gefriermikrotom erzielt und ein Teil der Präparate zur Mikrosezierung verwandt In allen untersuchten Muskeln befanden sich Fasern mit vielfacher Innervation (70 80% in dem M vocalis, 50% ungefähr in dem M cricotireoideus und in dem M crico aritenoideus lateralis, 5% ungefähr in dem M crico aritenoideus dorsalis) Keine Faser des M vocalis setzt sich an die Ligamenta vocalia an Nur in dem M vocalis befinden sich neuromuskulare Spindeln während in allen vier Muskeln propriozeptive Ausdehnungen der Art „spiral nerve ending" zu finden sind

REFERENCES

AMATI, M., and PIRRO A F., 1955 Osservazioni istologiche sui rapporti fra il muscolo ed il legamento vocale nell uomo *Boll Soc Ital Biol Sper* *31* 1068

BEHRINGER S., 1955 Die Anordnung der Muskulatur in der menschlichen Stimmlippe und im Gebiet des Conus Elasticus' *Z Anat Entwickl Gesch* *118* 324

BERENDES H., 1950 Neue anatomische Grundlagen zur Physiologie und Pathologie der Stimmlippenspannung *Arch Ohr Nas Kehlkopfheilk* *158* 371

BERG VAN DEN, JW., and MOLL, J., 1955 Zur Anatomie des menschlichen M vocalis Z Anat Entwickl Gesch *118* 465

BERTELLI D., 1922 *Trattato di Anatomia Umana* Milano

BIANCONI R., and MOLINARI G., 1962 Electroneurographic evidence of muscle spindles and other sensory endings in the intrinsic laryngeal muscles of the cat *Acta Otolaryng* (Stockh) 55 253

BORGUZZI A., 1961 Rassegna della letteratura relativa ai rapporti intercorrenti tra muscolo e legamento vocale *Boll Mal Orecch* 69 18

BRASH J C 1941 *Cunningham s Text Book of Anatomy* Oxford

CHIARUGI G., 1948 *Istituzioni di Anatomia dell uomo* Milano

CHRISTENSEN F., 1959 Topography of terminal motor innervation in striated muscles from stillborn infants *Amer J Phys Med* *38* 65

CILIMBARIS, P A 1910 Histologische Untersuchungen über die Muskelspindeln der Augenmuskulatur *Arch Mikr Anat* *75* 692

COËRS, C., 1953 Contribution à l etude de la jonction neuro musculaire II Topographie zonale de l innervation motrice terminale dans les muscles striés *Arch Biol* (Liège) 64 495

1955 Les variations structurelles normales et pathologiques *de la jonction neuro musculaire* *Acta Neurol Belg* 55 741

1955 Structural organization of the motor nerve endings in mammalian muscle spindles and other striated muscle fibres *Amer J Phys Med* *28* 166

COUTEAUX R., 1958 Remarques sur les méthodes actuelles de la détection histochimique des activités cholinestérasiques *Arch Int Physiol* *59* 526

1953 Particularités histochimiques des zones d insertion du muscle strié *C R Soc Biol* Paris *14* 1974

COUTEAUX R and TAXI J., 1952 Recherches histochimiques sur la distribution des activités cholinestérasiques au niveau *de la synapse* myoneurale *Arch Anat Micr Morph Exp* *41* 352

DESMEDT J E 1958 Méthodes d étude de la fonction neuro-musculaire chez l homme Myogramme isométrique électromyogramme d excitation et topographie de l innervation terminale *Acta Neurol Belg.*, *58* 977

FIZI C 1923 Anatomie des Kehlkopfes und des Tracheobronchialbaumes In *Handbuch der Hals Nasen und Ohrenheilk* Berlin München

FAVARO G 1935 *Trattato di Anatomia sistematica* Torino

FAZZARI I, 1948 *Anatomia sistematica dell uomo* Milano

FERNAND V S V and YOUNG J Z 1951 The size of the nerve fibres of muscle nerves *Proc Roy Soc B* 139, 35

GALLETTI C, 1962 Il muscolo vocale umano e i fusi neuromuscolari Studio micro e microscopico *Otorinolaring Ital* 31 212

GEGENBAUR C 1885 *Lehrbuch der Anatomie des Menschen* Leipzig

GEREBTZOFF, M A, 1953 Recherches histochimiques sur les acetilcholines et cholinesterases *Acta Anat* (Basel) 19 366

—1954 Appareil cholinestérasique à l insertion tendineuse des fibres musculaires striées *C R Soc Biol* (Paris) 148 632

GEREBTZOFF M A and LIEVENS E 1954 Presence d appareils cholinesterasiques musculo tendineaux chez divers Mammifères notamment chez l Homme et leur persistence apres denervation *C R Soc Biol* (Paris), 148 1896

GEREBTZOFF, M A and LIBACK G 1959 Le problème des muscles lents et rapides du larynx *Acta Otorhinolaryng Belg* 13 339

GIACOMINI C 1892 Annotazioni sull anatomia del negro *G Accad Med Torino* 40 17

GINSBORG B L 1959 Multiple innervation of chick muscle fibres *J Physiol* (Lond) 148 50

GINSBORG B L and MACKAY B 1961 A histochemical demonstration of two types of motor innervation in Avian skeletal muscle *Bibl Anat* (Basel) 2 173

GOERTTLER K 1948 Die Anordnung Histologie und Histogenese der quergestreiften Muskulatur im menschlichen Stimmband *Klin Wschr* 126

— 1951 Die Anordnung Histologie und Histogenese der quergestreiften Muskulatur im menschlichen Stimmband *Z Anat Entwickl Gesch* 115 352

1961 Spezifische myofibrillare Endorgane in der Wand der menschlichen Glottis *Arch Ohr Nas Kehlkopfheilk* 178 313

GRUTZNER P 1879 *Physiologie der Stimme in Sprache In Handbuch der Physiologie* vol 2 Leipzig

HAGGQUIST G 1956 *Gewebe und Systeme der Muskulatur* Berlin Göttingen Heidelberg

HENLE J 1873 *Handbuch der systematischen Anatomie des Menschen* Leipzig

HOLMSTEDT B 1957 *a* A modification of the thiocholine method for the determination of cholinesterase I *Biochemical evaluation of selective inhibitors* *Acta Physiol Scand* 40 322

— 1957 *b* *A modification of the thiocholine method for the determination of cholinesterase* II Histochemical application *Acta Physiol Scand* 40 331

JACOBSOHN A 1887 *Zur Lehre vom Bau und der Funktion des M thyreoarytenoideus beim Menschen Arch Mikr Anat* 29 617

KANTHACK A A 1889 *Zur Histologie der Stimmbänder Virchows Arch Path Anat* 118 137

KOELLE G B, and FRIEDENWALD S J, 1949 A histochemical method for localizing cholinesterase activity *Proc Soc Exp Biol* N Y 70 617

KONIG W F, 1961 Neuere Erkenntnisse uber die motorischen und sensiblen Nervenendungen im Vocalissystem des Menschen *Arch Ohr Nas Kehlk Kopfheilk* 178 316

KONIG W F, and VAN LEDEN H, 1961 *a* The peripheral nervous system of the human larynx II The vocalis muscle *Arch Otolaryng* (Chic) 74 153

— 1961 *b* The peripheral nervous system of the human larynx III The development *Arch Otolaryng* (Chic) 74 494

KUFFLER S W, and VAUGHAN WILLIAMS E M 1953 Small nerve junctional potentials The distribution of small motor nerves to frog skeletal muscle and the membrane characteristics of the fibres they innervate *J Physiol* (Lond) 121 289

Kuffler, C., 1960 Motor innervation of extraocular muscle *J Physiol* (Lond), *153*, 522
Lanz, von T., and Mayet, A., 1959 Zur Morphologie der Nervenendungen am quergestreiften Muskel Untersuchungen am M thyreoarytenoideus des Menschen *Z Anat Entwickl Gesch*, *121*, 116
Lasagna, F., 1914 Ricerche anatomiche sul muscolo vocale *Boll Soc Med Parma 12*, 210
Lauth, E A., 1837. *Nouveau manuel de l'Anatomiste* Bruxelles
Laskov, V F., 1955 Die Morphologie der Receptoren der eigenen Muskeln des Kehlkopfs *Arch Anat* (Moskva), *32*, 29
Lucas Keene M F., 1961 Muscle spindles in human laryngeal muscles *J Anat* (Lond), *95* 25
Ludwig, C., 1858 *Lehrbuch der Physiologie des Menschen* Leipzig
Luschka, von H., 1871 *Der Kehlkopf des Menschen*, Tubingen
Mayet, A., 1955 *a* Bau und Funktion des M vocalis und seine Beziehungen zu Lig vocale und Conus elasticus *Acta Anat* (Basel), *24*, 15
— 1955 *b* Zur funktionellen Anatomie der menschlichen Stimmlippe *Z Anat Entwickl Gesch 119*, 87
Masjome T., 1959 The anatomical studies on the laryngeal muscles of Japanese *J Jap Otorhinolaryng Soc*, *62*, 1890
Marco J., and Lopez de la Torre, M., 1962 Étude du muscle de la corde vocale a la lumière polarisée parallèle *Rev Laryng* (Bord), *83* 1053
Merkel, C L., 1901 *Anatomie und Physiologie des menschlichen Stimm und Sprachorgans* Leipzig
Molinari G A., 1962 *a* Studio elettroneurografico sulla distribuzione dei recettori in connessione con le fibre sensitive del nervo ricorrente *Otorinolaring Ital 31*, 68
— 1962 *b* La fisiologia del nervo ricorrente Studio elettroneurografico *Boll Soc Ital Fon 11* 121
Moller J., 1901 Beitrage zur Kenntnis der Kehlkopfmuskulatur *Arch Laryng Rhin* (Berl) *12* 304
Motta G., 1954 La muscolatura della corda vocale vera Ricerche sperimentali *Otorinolaring Ital*, *22*, 146
Mündnich K 1937 Untersuchungen uber den Bau der Nervenendungen in M vocalis und M posticus des Kaninchenlarynx *Z Hals Nas Ohrenheilk 41*, 235
Murray J G., 1957 Innervation of the intrinsic muscles of the cat's larynx by the recurrent laryngeal nerve a unimodal nerve *J Physiol* (Lond), *135* 206
Negus, V E., 1929 *The Mechanism of the Larynx* London
Nemai J., 1937 Function of vocal organs *Mschr Ohrenheilk 71* 671
Orlandini A., 1916 Contributo allo studio dei muscoli della laringe e delle loro varieta *Arch Ital Otol 27* 373
Paulsen K., 1958 Über Vorkommen und Zahl von Muskelspindeln in inneren Kehlkopfmuskeln des Menschen *Z Zellforsch 48* 349
Pennetta G., 1959 L innervazione sensitiva del muscolo vocale *Arch Ital Laring*., *67*, 255
Piquet J., and Babbets, A., 1960 Observations sur l'innervation motrice du muscle vocal *Acta Otolaryng* (Stockh) *51* 203
Piquet J M., Hoffman and Husson R., 1937 Recherches histologiques sur le nerf recurrent et sur les plaques motrices de la musculature laryngée intrinsique de l'homme *J Franç Otorhinolaryng 6* 235
Pressman J J., 1942 Physiology of the vocal cords in phonation and respiration *Arch Otolaryng* (Chic) *35* 355
Rauber A 1902 *Lehrbuch der Anatomie des Menschen* Leipzig
Roncallo P., 1939 Ricerche sul modo di inserzione delle fibre del muscolo vocale sul ligamento vocale *Arch Ital Anat Embriol*., *41*, 337

ROUVIÈRE H., 1924 *Anatomie humaine* Paris
RUDOLPH G 1960 Multiple Innervation von Muskelfasern im M vocalis des Menschen *Experientia 16* 551
— 1961 Spiral nerve endings (proprioceptors) in the human vocal muscle *Nature (Lond)*, *190* 726
— 1962 Particularités des synapses neuro musculaires dans le muscle vocal de l'homme *Rev Laryng* (Bord) 83 569
RUEDI L 1959 Some observations on the histology and function of the larynx *J Laryng* 73 1
RUHLMANN A 1874 Untersuchungen über das Zusammenwirken der Muskeln bei einigen häufiger vorkommenden Kehlkopfstellungen *Wien Sitzungsberichte 69* 59
SAPPEY C 1877 *Traité d'Anatomie descriptive* Paris
SCHMIDT L 1934 Über den feineren Bau einiger Muskeln des Menschen *Z Mikr Anat Forsch 36* 215
SCHLOSSHAUER B., and VOSTEEN K H 1957 Über die Anordnung und Wirkungsweise der im Conus elasticus ansetzenden Fasern des Stimmmuskels *Z Laryng Rhin* [illegible]
— 1958 Über den Verlauf und die Funktion der Stimmmuskelfasern *Z Anat Entwickl Gesch 120* 456
SCHWARZACHER H G 1959 Über die Länge und Anordnung der Muskelfasern in menschlichen Skeletmuskeln *Acta Anat* (Basel) 37 217
SEILER G 1956 Embryologie comparée des cordes vocales *Rev Laryng* (Bord) [illegible] 408
SHATTOCK S G., 1881 Note on the anatomy of the thyro arytenoid muscle in the human larynx *J Anat Physiol 15* 356
SIMONETTA B 1929 Studio comparativo sul muscolo tiro aritenoideo e sul ligamento vocale con particolare riguardo all'inserzione del muscolo sul legamento ed alla struttura di alcune parti del legamento stesso e con osservazioni sullo sviluppo del processo mediano della cartilagine tiroide dell'uomo *Ric Morf* 9 21
SONESSON B 1960 On the anatomy and vibratory pattern of the human vocal folds *Acta Otolaryng* (Stockh) Suppl 156
TAVANI L 1935 Rapporti del muscolo tiro aritenoideo con il legamento vocale in alcune scimmie platirrine *Monit Zool Ital 46* 141
TERRACOL J and ARDOUIN P 1964 Les fuseaux et les globes sensitifs du larynx *Acta Otolaryng* (Stockh) 57 320
TERRACOL J GUERRIER Y., and CAMUS L., 1956 Le sphincter glottique étude anatomo clinique *Ann Otolaryng* (Paris) 73 451
TERRACOL J., and GUERRIER H L., 1953 La musculature de la corde vocale *Rev Laryng* (Bord) 74 317
TESTUT L., 1923 *Trattato di Anatomia umana* Torino
VOSTEEN K H., 1957 Recherches histologiques en lumière polarisée sur la musculature des cordes vocales *Rev Laryng* (Bord) 78 608 (Suppl)
WINCKLER G 1957 Les différentes critères de l'innervation proprioceptive des muscles du larynx chez l'homme *Arch Anat* (Strasbourg) 25 37
WUSTROW F., 1952 Bau und Funktion des menschlichen M vocalis *Z Anat Entwickl Gesch 116* 506
— 1956 Zur Anatomie des M vocalis *Z Laryng Rhinol* [illegible]
ZENKER W., 1963 Unterschiede im Strukturbild der myoneuralen Synapsen und im Faseraufbau des M Thyreoarytaenoides des Menschen und des Rhesusaffen *Anat Anz 112* Suppl *12*
ZWIRNER R., 1958 Beitrag zur Innervation des Kehlkopfes *Z Mikr Anat Forsch 64* 685

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HISTOLOGISCHE UNTERSUCHUNGEN ÜBER AUTOTRANSPLANTIERTE GEHÖRKNÖCHELCHEN UND KNOCHENSTÜCKCHEN IM MITTELOHR BEIM MENSCHEN

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Fassen wir die Ergebnisse unserer Untersuchungen zusammen, so lässt sich feststellen, dass sowohl die Gehörknöchelchentransplantate als auch die frei transplantierten Knochenstücke reizlos eingeheilt und über Bindegewebsbrücken, selbst wenn diese nur kleinflächig, ausreichend ernährt waren. Veränderungen der Knochengrobstruktur waren in keinem Fall zu beobachten. Knochenwundflächen hatten sich mit einem Epithel überzogen. An vier von neun autotransplantierten Gehörknöchelchen waren lakunäre und arrosive Abbauprozesse nachweisbar, deren Ausmass in keiner Beziehung zur Transplantationsdauer stehen. Es gibt Hinweise dafür, dass diese Abbauprozesse nicht Folge der Transplantation, sondern vielmehr durch die schon vor der Verpflanzung vorhandene Mittelohrentzündung verursacht waren.

Gehörknöchelchen und Knochenstücke sind gegenüber der freien Autotransplantation im Bereiche des Mittelohres also sehr widerstandsfähig und für die Bildung einer Columella oder zur Überbrückung von Defekten der Gehörknöchelchenkette geeignet. Die Sorge einer Erweichung durch Mangelernährung ist nicht berechtigt, da der nach der Transplantation einsetzende Stoffwechsel ausreicht, um den Knochen am Leben zu erhalten.

Das Problem der Autotransplantation von Gehörknöchelchen und Knochenstücken ist also nicht dieser Art, sondern besteht darin, wie man einerseits einen guten funktionellen Kontakt herstellen und andererseits die Bildung von unerwünschten Adhäsionen zur Umgebung vermeiden kann.

Sowohl bei der Tympanoplastik als auch bei der Stapeschirurgie ergeben sich für den Operateur immer wieder Situationen, Defekte der Gehörknöchelchen zu überbrücken oder aber eine vereinfachte Schalldrucktransformation durch eine Columella (Zöllner) herzustellen.

Die ersten Versuche, einen Ersatzsteigbügel zu transplantieren, gehen auf Wullstein zurück, der 1952 ein aus Palavit geformtes Ersatzstück zwischen Transplantat und Stapesfussplatte einsetzte. Später hat er aus Hammerkopf oder Amboss autoplastische Transplantate geformt und sie in der

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Rouvière H., 1924 *Anatomie humaine* Paris
Rudolph G., 1960 Multiple innervation von Muskelfasern im M. vocalis des Menschen *Experientia 16* 551
— 1961 Spiral nerve endings (proprioceptors) in the human vocal muscle *Nature* (Lond.), *190* 726
— 1962 Particularités des synapses neuro musculaires dans le muscle vocal de l'Homme *Rev Laryng* (Bord.) 83 369
Rueedi L., 1959 Some observations on the histology and function of the larynx *J Laryng* 73 1
Ruehlmann A 1874 Untersuchungen über das Zusammenwirken der Muskeln bei einigen häufiger vorkommenden Kehlkopfstellungen *Wien Sitzungsberichte 69*
Sappey C 1877 *Traité d'Anatomie descriptive* Paris
Schimert, J., 1934 Über den feineren Bau einiger Muskeln des Menschen *Z Mikr Anat Forsch 36* 215
Schlossauer B., and Vosteen K H 1957 Über die Anordnung und Wirkungsweise der im Conus elasticus ansetzenden Fasern des Stimmuskels *Z Laryng Rhinol* 36 ...
— 1958 Über den Verlauf und die Funktion der Stimmuskelfasern *Z Anat Entwickl Gesch 120* 456
Schwarzacher, H G 1959 Über die Länge und Anordnung der Muskelfasern in menschlichen Skeletmuskeln *Acta Anat* (Basel) 37 217
Seiter G 1956 Embryologie comparée des cordes vocales *Rev Laryng* (Bord.) 77 408
Shattock S G., 1881 Note on the anatomy of the thyro arytenoid muscle in the human larynx *J Anat Physiol 15* 356
Simonetta B., 1929 Studio comparativo sul muscolo tiro aritenoideo e sul ligamento vocale con particolare riguardo all'inserzione del muscolo sul legamento ed alla struttura di alcune parti del legamento stesso e con osservazioni sullo sviluppo del processo mediano della cartilagine tiroide dell'uomo *Ric Morf 9* 21
Sonesson B., 1960 On the anatomy and vibratory pattern of the human vocal folds *Acta Otolaryng* (Stockh.) Suppl *156*
Tavani L., 1935 Rapporti del muscolo tiro aritenoideo con il legamento vocale in alcune scimmie platirrine *Monit Zool Ital 46* 141
Terracol J and Ardouin P., 1964 Les fuseaux et les globes sensitifs du larynx *Acta Otolaryng* (Stockh.) 57 320
Terracol J Guerrier Y., and Camps, F., 1956 Le sphincter glottique étude anatomo clinique *Ann Otolaryng* (Paris) 73 451
Terracol J., and Guibert H L., 1953 La musculature de la corde vocale *Rev Laryng* (Bord.) 74 317
Testut L., 1923 *Trattato di Anatomia umana* Torino
Vosteen K H., 1957 Recherches histologiques en lumière polarisée sur la musculature des cordes vocales *Rev Laryng* (Bord.) 78 608 (Suppl
Winckler G., 1957 Les différentes critères de l'innervation proprioceptive des muscles du larynx chez l'homme *Arch Anat* (Strasbourg) 25 37
Wustrow F 1952 Bau und Funktion des menschlichen M. vocalis *Z Anat Entwickl Gesch 116* 506
— 1956 *Zur Anatomie des M vocalis Z Laryng Rhinol* 35 126
Zenker W 1963 Unterschiede im Strukturbild der myoneuralen Synapsen und im Faseraufbau des M Thyreoarytenoides des Menschen und des Rhesusaffen *Anat Anz 112* Suppl *12*
Zwirner R., 1958 Beitrag zur Innervation des Kehlkopfes *Z Mikr Anat Forsch 64* 685

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Rudolph, G., 1960 Multiple innervation von Muskelfasern im M. vocalis des Menschen *Experientia 16*, 551

— 1961 Spiral nerve endings (proprioceptors) in the human vocal muscle *Nature (Lond.)*, *190* 726

— 1962 Particularités des synapses neuro musculaires dans le muscle vocal de l'Homme *Rev Laryng* (Bord) 83 569

Rueda L., 1959 Some observations on the histology and function of the larynx *J Laryng* 73 1

Rühlmann, A. 1874 Untersuchungen über das Zusammenwirken der Muskeln bei einigen häufiger vorkommenden Kehlkopfstellungen *Wien Sitzungsberichte* 69 59

Sappey, C., 1877 *Traité d'Anatomie descriptive* Paris

Schmidt, J. 1934 Über den feineren Bau einiger Muskeln des Menschen *Z Mikr Anat Forsch* 36 215

Schlossauer, B and Vosteen, K H., 1957 Über die Anordnung und Wirkungsweise der im Conus elasticus ansetzenden Fasern des Stimmuskels *Z Laryng Rhinol* 36 642

— 1958 Über den Verlauf und die Funktion der Stimmuskelfasern *Z Anat Entwickl Gesch* *120* 456

Schwarzacher, H G., 1959 Über die Länge und Anordnung der Muskelfasern in menschlichen Skelettmuskeln *Acta Anat (Basel)*, *37* 217

Spiter G 1956 Embryologie comparée des cordes vocales *Rev Laryng* (Bord) 77 408

Shattock, S G 1881 Note on the anatomy of the thyro arytenoid muscle in the human larynx *J Anat Physiol* 15 356

Simonetta B 1929 Studio comparativo sul muscolo tiro aritenoideo e sul legamento vocale con particolare riguardo all'inserzione del muscolo sul legamento ed alla struttura di alcune parti del legamento stesso e con osservazioni sullo sviluppo del processo mediano della cartilagine tiroide dell'uomo *Ric Morf* 9 21

Sonesson B 1960 On the anatomy and vibratory pattern of the human vocal folds *Acta Otolaryng* (Stockh) Suppl *156*

Tavani L 1935 Rapporti del muscolo tiro aritenoideo con il legamento vocale in alcune scimmie platirrine *Monit Zool Ital* 46 141

Terracol J and Ardouin P 1964 Les fuseaux et les globes sensitifs du larynx *Acta Otolaryng* (Stockh) 57 320

Terracol J Guerrier Y and Camps F 1956 Le sphincter glottique étude anatomo clinique *Ann Otolaryng* (Paris) 73 451

Terracol J and Guibert H L., 1953 La musculature de la corde vocale *Rev Laryng* (Bord) 74 317

Testut L 1923 *Trattato di Anatomia umana* Torino

Vosteen K H., 1957 Recherches histologiques en lumière polarisée sur la musculature des cordes vocales *Rev Laryng* (Bord) 78 608 (Suppl)

Winckler G., 1957 Les différentes critères de l'innervation proprioceptive des muscles du larynx chez l'homme *Arch Anat* (Strasbourg) 25 37

Wustrow F 1952 Bau und Funktion des menschlichen M vocalis *Z Anat Entwickl Gesch* *116* 506

— 1956 Zur Anatomie des M vocalis *Z Laryng Rhinol* 35 126

Zenker W., 1963 Unterschiede im Strukturbild der myoneuralen Synapsen und im Faseraufbau des M Thyreoarytenoides des Menschen und des Rhesusaffen *Anat Anz* *112* Suppl *12*

Zwirner R 1958 Beitrag zur Innervation des Kehlkopfes *Z Mikr Anat Forsch* 64 685

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auch dann vor, wenn bei der Stapesinterposition das Stapesfragment vorübergehend ganz aus dem Verband gelöst und später wieder reimplantiert wird Dieses Verfahren wird auch heute noch von verschiedenen Operateuren geubt, während die meisten Autoren das Amboss-Steigbügelgelenk möglichst schonen, nicht nur wegen des audiologischen Effektes, sondern auch zur Sicherstellung der Ernährung des Stapesfragmentes, andere erhalten die Stapediussehne als Ernährungsbasis

Hall & Rytzner haben 1956 über eine Methode der Stapedektomie berichtet bei welcher sie gleichzeitig eine freie Transplantation von Gehörknöchelchen oder von Teilen derselben vorgenommen haben Auf Grund von Reexplorationen mit histologischen Untersuchungen von 3 Fällen (1960) sind sie zu der Ansicht gelangt, dass die Ernährung des transplantierten Gehörknöchelchens uber die Schleimhaut gewährleistet ist M Portman & G Ceresia haben 1959 eine Methode zur Rekonstruktion des Steigbügels aus dem Knochen der Gehörgangswand mitgeteilt und 1960 hat Zöllner eine Technik angegeben zur Formung einer Columella aus periostalem Knochen Er gewinnt die gewunschte Form durch Ausfräsen aus der Corticalis des Mastoids und schafft zusätzlich vertiefte Gelenkpfannen oder -platten und gabelförmige Widerlager zur besseren Verankerung der Stucke, die als Steigbugelersatz zwischen ovales Fenster und Amboss oder aber auch zwischen ovales Fenster und Trommelfell als Columella eingefügt werden

Beck & Franz konnten zeigen, dass dieser frei transplantierte Knochenspan nach Zöllner von Schleimhaut überzogen und auf diesem Wege ausreichend ernahrt wird, um ihn am Leben zu erhalten Die Beobachtung beim Menschen (3 Fälle) erstrecken sich uber einen Zeitraum bis zu 150 Tagen Im Tierexperiment liessen Autotransplantate beim Meerschweinchen nach 97 Tagen eine volle Vitalität des Corticalisspans mit regen Um- und Anbauvorgangen erkennen Belucci & Wolff fanden bei Katzen, dass der trans plantierte Stapes überlebt, sahen aber häufig narbige Verwachsungen zur Umgebung

Experimentell haben sich mit dem Schicksal einer Knochencolumella auch Musebeck & Falk (1963) beschaftigt Bei Kaninchen haben sie den Steigbügel ganz aus dem Verband gelöst und wieder eingesetzt, in anderen Fallen den Stapes durch einen Knochenspan aus der Bulla ersetzt Sie konnten histologisch feststellen, dass nach Zeiträumen bis zu 12 Monaten die autotransplantierten Steigbugel wenig die Bullaspane jedoch stark umgebaut worden waren Von letzteren wies die Halfte einen Vitalitätsverlust auf Resorptionserscheinungen waren im ambossnahe gelegenen Teil des Knochenspanes starker als in jenem Teil, der dem Vestibulum zugekehrt war Neuer Knochen war an jenen Stellen gebildet worden, die im unmittelbaren Druckbereich der Schalleitung lagen im Schallschatten war die Knochenneubildung nur ganz gering oder blieb ganz aus Die neuen Knochenstrukturen waren zur Schallachse gerichtet und wurden von Müsebeck & Falk deshalb als „knocherne Druckstrukturen" gedeutet

Über histologische Untersuchungen an frei autotransplantierten Gehör-

Paukenhöhle bei Tympanoplastiken verwendet, dieses Verfahren aber wieder aufgegeben, da er fürchtete, dass die Ernährung solch freier Knochenautotransplantate nicht ausreichen würde.

Auch Zöllner hegte diese Befürchtungen, als er 1955 die Interposition des Ambosskörpers zwischen Stapeskopf und Hammerhals zur Überbrückung eines Defektes des langen Ambossschenkels beschrieb. Er versuchte wenigstens eines der ernährenden Bänder zu erhalten. Im gleichen Jahre hat W. Kley zur Zweckmässigkeit einer Kunststoffcolumella bei der Tympanoplastik Stellung genommen und Fälle mitgeteilt, bei welchen Knochentransplantate aus Resten der Gehörknöchelchenkette (Amboss oder Hammerkopf) verwendet worden waren. Die Resultate bezüglich des Hörvermögens waren nicht immer befriedigend. Wie Nachoperationen zeigten, war es bei den audiologischen Misserfolgen zu Verlagerungen gekommen, oder aber zu breiten Adhaesionen am Facialiswulst über dem ovalen Fenster. In keinem Falle wurde jedoch eine Erweichung oder Zerstörung des freien Implantates beobachtet, auch wenn das Gehörknöchelchen für die Aufgabe als Columella durch Zurechtschleifen erst geformt worden war.

Wegen der Unzuverlässigkeit des audiologischen Resultates haben Wullstein und Kley später den Aufbau eine Typ IV bevorzugt und nur in jenen Fällen noch das Columellasystem mit Hilfe eines Gehörknöchelchens angewandt, bei welchen die Schleimhautverhältnisse so schlecht waren, dass bei der Bildung einer „kleinen" Pauke (wie beim Typ IV) die Gefahr der Ausbildung eines Adhaesivprozesses zu gross war. Nach Abheilen der Pauke und schlechtem Hörergebnis wurde dann revidiert und die Plastik zu einem Typ IV umgewandelt, nachdem sich die Paukenschleimhaut erholt hatte. Ein Teil des unseren jetzigen Untersuchungen zugrunde liegenden Materials stammt von solchen Operationen.

Mit der Stapedektomie ist die Frage nach einem zweckmässigen Stapesersatz erneut akut geworden, insbesondere dann, wenn der Steigbügel so ungünstig frakturiert, dass er für die Schalldrucktransformation nicht mehr verwendet werden kann. Aber auch in Fällen entzündlicher oder otosklerotischer Stapesfixation bei gleichzeitigem Fehlen der Stapesschenkel (z. B. bei früherem missglückten Mobilisationsversuch) oder gleichzeitiger Unterbrechung der Kette an anderer Stelle kann man genötigt werden, ein Columellasystem aufzubauen, um wieder eine Schalldrucktransformation herzustellen und die Fenestration im Bogengang oder im ovalen Fenster ohne Schalldrucktransformation zu umgehen.

Im Rahmen dieses Beitrages wollen wir absichtlich nicht auf die verschiedenen Möglichkeiten des Ersatzes von Gehörknöchelchen durch Kunststoffe (Wullstein: Palavit, Polycarbonat, Shea: Polyaethylen, Teflon, Schuknecht: Rostfreier Draht) oder körpereigenes Gewebe wie Knorpel (Utech, J. Heermann), Bindegewebe (Zangemeister, H. Heermann) eingehen, sondern uns nur mit der Transplantation von Gehörknöchelchen (Wullstein, Zöllner, Kley, Hall & Rytzner) oder von Knochenstücken (Zöllner) befassen.

Der Fall einer freien Autotransplantation im weitgefassten Sinne liegt





Abb 3 D Rita Amboss 9½ Stunden nach Dislokation bei Attrotomie Arrodierende Knochenlakune am Processus lenticularis

Abb 4 D Helga Knochensplitter 8 Jahre nach Autotransplantation"

I Untersuchungen an frei und autotransplantierten Gehörknöchelchen

Um eine unmittelbare Vergleichsmöglichkeit mit „normalen" Gehörknöchelchen zu haben hat W Draf noch eine Anzahl von Gehörknöchelchen aus frischen Leichenfelsenbeinen histologisch aufgearbeitet Im übrigen beziehen wir uns auf die Untersuchungen an Gehörknöchelchen von Eckert Möbius und auf die ausführlichen Arbeiten in neuerer Zeit von F Wustrow

Danach finden sich in Hammer und Amboss verkalkte Knorpelreste mit Globuli ossei welche bei der enchondralen Ossifikation durch Ablagerung von Knochensubstanz in Hohlräume die früher von Knorpelzellen eingenommen waren entstanden (Schaffer Erdheim O Mayer) Ferner lässt sich Strähnenknochen nachweisen wie ihn Max Meyer in der Labyrinthkapsel beschrieben hat Geflechtartiger Knochen (Gegenbauer v Ebner) liegt wenn er in den Ossicula überhaupt vorhanden ist vorwiegend in den Randpartien Schliesslich lässt sich beim Erwachsenen stets in grösserer Ausdehnung Lamellenknochen finden Im Inneren der Compacta von Hammer und Amboss sind individuell verschieden grosse Markräume eingelagert Eine Spongiosa mit Knorpelresten wie dies Eckert Möbius beschreibt soll nach Wustrow nicht vorhanden sein Auch wir konnten solche Spongiosaräume in unseren Schnitten nicht finden Nach aussen hin sind die Ossicula mit einem dünnen Periost und einem zarten Epithel überzogen In einzelnen Fällen konnte W Draf auch an nicht transplantierten Gehörknöchelchen kleine Lakunen nachweisen

Schon normalerweise ist also das histologische Bild der Gehörknöchelchen verschiedener Menschen nicht einheitlich Dies muss bei der Beurteilung der transplantierten Ossicula berücksichtigt werden

Makroskopisch und bei der Betrachtung unter dem Operationsmikroskop erschienen alle transplantierten Gehörknöchelchen oder Teile derselben reizlos eingeheilt Zur Umgebung waren *bindegewebige Brücken* teilweise auch mehr oder weniger breitflächige *Narbenmembranen* entstanden In einem Fall eines ausserhalb als Columella autotransplantierten Hammers





Abb. 1. St. Johanna. Amboss 2 Jahre aus dem Verband gelöst. Zweimal „autotransplantiert“.
Abb. 2. L. Hildburg. Hammergriff 3 Monate nach Autotransplantation als Columella.

Knöchelchen oder ins Mittelohr frei transplantierten Knochenteilen beim Menschen liegen unseres Wissens ausser den Fällen von Hall & Rytzner sowie von Beck & Franz bisher keine Mitteilungen vor. Das von uns untersuchte Material umfasst insgesamt 13 freie Transplantate, und zwar 10 Gehörknöchelchen oder Teile derselben und 3 Knochenstücke. Ein Transplantat wurde schon 96 Stunden nach der Verpflanzung wieder entnommen, die anderen waren einige Monate, meist aber mehrere Jahre eingeheilt und in einem Fall lag die Transplantation sogar 10 Jahre zurück.

Bei den Gehörknöchelchen handelte es sich, wie aus der Tabelle hervorgeht, teils um Transplantate, die als Columella eingesetzt waren, bei einer Revisionsoperation wegen audiologischen Misserfolges aber wieder entfernt wurden, oder aber um Ambossknöchelchen, die anlässlich einer Antrotomie oder eines Schädeltraumas mit Schläfenbeinfraktur luxiert, völlig aus dem Verband gelöst und irgendwo im Mittelohr liegen geblieben waren. Sie wurden bei dem Eingriff zur Hörverbesserung entfernt. In zwei Fällen war der Incus, der nach einer Antrotomie verschleppt und im einen Fall im Antrum, im anderen im Mesotympanon eingeheilt war, zwischen Hammerkopf und Stapes reimplantiert, wegen schlechten audiologischen Resultates aber später wieder entfernt worden. Diese beiden Knöchelchen waren also *zweimal den Bedingungen der freien Transplantation unterworfen*.

Schliesslich haben wir noch drei Knochenstücke untersucht, die bei früher vorgenommenen Operationen (Fenestration im Bogengang bzw. Radikaloperation) verschleppt und ungewollt „autotransplantiert“ wurden.

Bei unseren Untersuchungen haben wir auf folgende Gesichtspunkte geachtet:

1. Postoperative Einheilung,
2. Ernährung des Transplantates,
3. Schleimhautüberzug,
4. Veränderungen der *Knochengrobstruktur*,
5. Abbauvorgänge.

G. Marianne 60 Jahre	Ot. med. chron. mit Defekt des langen Ambossschenkels, des Hammergriffs und des Stapesbogens. 18. 3. 1963 Tympanoplastik. Ambosskörper und Hammerkopf als Columella eingesetzt. 12. 7. 1963 Revision und Umwandlung in Typ IV	Ambosskörper	4 Monate	narbige Adhäsionen zur Umgebung	gut	war histologisch nicht aufzuarbeiten		Starke narbige Verwachsungen zum Facialiskanal
		Hammerkopf	4 Monate		gut	keine	nicht vorhanden	
W. Franz 12 Jahre	Otosklerose. 1956 Fenestration mit Durchtrennung des Hammerhalses. 1962 Platinektomie und Tympanoplastik Typ III, dabei verlagerten Hammerkopf entfernt	Hammerkopf	6 Jahre	reizlos	gut	keine	geringfügige Abbauvorgänge	
J. Hildburg 40 Jahre	Ot. med. chron. 3. 7. 1963 Tympanoplastik. Hammergriff als Columella eingesetzt. 3 Monate später Revision aus audiologischen Gründen	Hammergriff	3 Monate	reizlos	gut	keine	nicht vorhanden	Hammergriffcolumella durch Narbenzug verrutscht
M. Nassrin 21 Jahre	Ot. med. chron. 1961 und 1962 Tympanoplastik ausserhalb. Hammer als Columella zwischen Transplantat und fixierter Fussplatte eingesetzt. 3. 7. 1963 Platinektomie mit Hammercolumella	Hammer	mindestens 1 Jahr	reizlos	gut	nicht histologisch aufgearbeitet		Manubrium mallei mit freiem Ende knöchern am Rand des ovalen Fensters fixiert
D. Rita 10 Jahre	Ot. med. ac. mit Mastoiditis. Antrotomie. 4 Tage später Revision und Entfernung des dislozierten Amboss	Amboss	96 Stunden	umgebende Schleimhaut infiltriert	gut	keine	arrodierende Knochenlakune am Proc. lentiformis	Arrosion wahrscheinlich auf Otitis zurückzuführen

TABELLE 1

	Kurzanamnese	Autotransplantat	Zeitdauer nach der Autotransplantation	Postop. Einheilung	Ernährung	Veränderung der Knochengrobstruk.	Abbauvorgänge im histol. Schnitt	Besonderheiten und Ursache des audiologischen Misserfolges
Ph. Rudolf 36 Jahre	Ot. med. chron., 1957 Tympanoplastik Typ III mit Ambosscolumella, 1959 Revision und Umwandlung in Type IV	Amboss	21 Monate	reizlos	gut	keine	kleine Lakunen	Guter Kontakt der Columella zum Trommelfelltransplantat. Verkantung zur ovalen Nische durch Narbenzug
St. Johanna 46 Jahre	1960 Antrotomie, danach Schwerhörigkeit. Tympanoskopie am 2.2.1962. Amboss liegt im oberen Durchlüftungsweg, wird reimplantiert. Revision am 11.2.1962 und Umwandlung in Tympanoplastik Typ III aus audiologischen Gründen	Amboss	2 Jahre	reizlos	gut	keine	nicht vorhanden	Die bindegewebige Verbindung zum Stapeskopf war nach der Reimplantation zu locker (Kontaktschwäche). Amboss zweimal autotransplantiert
Fr. Helmut 21 Jahre	1956 Antrotomie mit Luxation des Amboss. 15.7.1960 Tympanoskopie und Reimplantation des Amboss. 7.9.1960 Tympanoplastik Typ III aus audiologischen Gründen	Amboss	4 Jahre	reizlos	gut	keine	nicht vorhanden	Kontaktschwäche zum Stapes
Ob. Franz 57 Jahre	Ot. med. chron. mit Defekt des langen Ambosschenkels. Tympanoplastik 31.5.1961. Amboss zwischen Hammerhals und Stapeskopf interponiert. Revision und Umbau in Typ III am 5.6.1963	Ambosskörper	25 Monate	narbige Adhäsionen	gut	keine	oberflächliche Arrosionen und Lakunen in Verbindung mit zentr. Markhöhle. Umgebend Bindegewebe infiltriert	Proc. lentiformis war vor Autotransplantation des Ambosses schon entzündlich mazeriert

konnten wir *keine Umbauvorgänge in der Art von Druckstrukturen* erkennen. Die häufigste Ursache des audiologischen Misserfolges nach der Transplantation waren Adhaesionen zur Umgebung oder Kontaktschwäche zu anderen Gehörknöchelchen.

II. *Untersuchungen an frei und autotransplantierten Knochenstücken*

An dieses Material kamen wir dadurch, dass wir bei Ohroperationen eingeheilte Knochensplitter in der Paukenhöhle fanden, die bei vorangegangenen Eingriffen dorthin verschleppt waren. In diesen Fällen sind also die Bedingungen einer freien Autotransplantation erfüllt. Zwar haben diese Knochenteile nicht als Columella fungiert und waren auch nicht in die Gehörknöchelchenkette eingebaut, so dass ein unmittelbarer Vergleich zur Zöllnerschen Knochenplastik bei der Stapedektomie nicht möglich ist; doch kann die histologische Struktur dieser vor Jahren transplantierten Knochenstücke Aufschluss darüber geben, wie der Knochen eine solche freie Verpflanzung überhaupt überlebt.

Da die Bedingungen des Transplantationsbettes in den drei Fällen verschieden waren, muss hier auf die Einzelheiten etwas näher eingegangen werden.

Im ersten Fall (M. Gertraude) wurde 10 Jahre nach der Bogengangsfenestration ein ins Hypotympanon verlagerter und dort eingeheilter Knochensplitter entfernt. Das Knochenstück hat Rautenform, ist etwa 2 mm lang und nahezu vollständig von Epithel überwachsen. Das System der Knochenlamellen ist erhalten, die Osteocythenkerne sind deutlich angefärbt. Von der Verwachsungsstelle mit dem Transplantationsbett ausgehend ist es durch einsprossendes Bindegewebe zu Abbauvorgängen gekommen. Das die Hohlräume ausfüllende zellreiche Bindegewebe ist stark vaskularisiert. Zeichen einer frischen Entzündung sind nicht vorhanden. Trotz der als Umbauvorgang zu deutenden Veränderungen hat dieses Knochenstück nur wenig von seiner eigentlichen Knochenstruktur eingebüsst.

Im zweiten Fall (D. Helga) handelt es sich um einen Knochensplitter, der anlässlich einer Radikaloperation autotransplantiert wurde und 3 Jahre eingeheilt war. Die Form dieses Knochenstückes weist darauf hin, dass es sich wahrscheinlich beim Meisseln zu einer Rolle geformt hat. Der zentrale Hohlraum ist nur teilweise mit lockerem Bindegewebe ausgefüllt, während die Aussenfläche des Knochensplitters grossenteils von einem Epithel überzogen ist. Die Knochenlamellen sind regelmässig angeordnet und in der Färbung scharf konturiert. Die Osteocyten sind mit ihren Fortsätzen gut zur Darstellung gelangt. Entzündliche Infiltrationen sind nicht festzustellen. Nur an einer Stelle ist eine Lakunenbildung nachweisbar, die aber bei der sonst völlig erhaltenen Gesamtstruktur als bedeutungslos angesehen werden kann.

Im dritten Fall (v. Br. Th.) handelte es sich um eine Otosklerose mit mehreren Revisionen. Bei der letzten Operation wurde ein Knochensplitter entfernt, der mindestens 2 Jahre aus dem Verband gelöst und autotransplantiert war. Die histologischen Untersuchungen zeigten eine gut erhaltene Knochenstruktur mit strähniger Lamellierung. Die Osteocytenkerne waren gut angefärbt und in

war es, wie sich bei der Revision zeigte, zu einer *knöchernen Verwachsung* des freien Endes des Manubrium mallei mit dem unteren Rand des ovalen Fensters gekommen. Eine histologische Untersuchung dieses Knöchelchens wurde nicht vorgenommen, da der Hammer bei der Nachoperation (Platinektomie wegen fixierter Stapesfussplatte) als Columella wiederverwendet wurde.

Die grobe Knochenstruktur des Transplantates war in allen Fällen erhalten. Selbst der Processus lentiformis des Amboss, der auf Grund klinischer Beobachtungen gegenüber Ernährungsstörungen besonders empfindlich zu sein scheint, war intakt, wenn es sich um die Autotransplantation eines unversehrten Incus gehandelt hatte. In zwei Fällen wurde der Amboss sogar zweimal völlig aus dem Verband gelöst und transplantiert, ohne dass es zu groben Defekten des Knöchelchens gekommen wäre.

Bei der *mikroskopischen Untersuchung* waren *Periost und Schleimhaut weitgehend erhalten.* Bei den Defekten des Epithels handelte es sich meist um Artefakte. Das Periost fehlte an jenen Stellen, wo Teile der Gehörknöchelchen abgetrennt worden waren. Die Wundflächen waren von Epithel oder Bindegewebe überzogen.

In den *Markräumen* der Knöchelchen waren *zahlreiche Blutgefässe* nachweisbar, mehr oder minder dicht mit Erythrocyten gefüllt.

Die *Osteocyten waren allgemein gut angefärbt,* was für die erhaltene Vitalität der Knochenzellen spricht. Aus diesen Beobachtungen darf man den Schluss ziehen, dass *die Ernährung der Knöchelchen ausreichend war,* auch wenn die Verbindung zur neuen Umgebung nur über schmale bindegewebige Brücken vonstatten ging.

Dennoch waren bei nahezu der Hälfte der transplantierten oder luxierten Gehörknöchelchen histologische Veränderungen in Form *oberflächlicher Arrosionen oder Lakunenbildungen* nachweisbar, die als Abbau- oder Umbauvorgänge gedeutet werden müssen. Beim Amboss fanden sich solche Lakunen besonders zahlreich im Bereiche des Proc. lentiformis, sie hatten aber in keinem Präparat zu einer die Kontinuität bedrohenden Destruktion geführt. Das Ausmass dieser Degenerationserscheinungen ist nicht mit der Dauer der Transplantation in Korrelation zu bringen. An nur kurzfristig eingeheilten Transplantaten sind die Abbauvorgänge teilweise deutlicher als bei den über längere Zeit eingeheilten Knöchelchen. Da in all diesen Fällen eine Mittelohrentzündung, akut oder chronisch, zum Zeitpunkt der Autotransplantation im Gange war, kann nicht entschieden werden, ob die Arrosionen Folge der Entzündung oder der Transplantation sind. Da wir in keinem Falle Osteoklasten nachweisen konnten, neigen wir zu der Ansicht, dass die Lakunenbildung eher als Folge der Otitis media anzusehen ist, zumal nicht alle transplantierten Ossicula solche Veränderungen aufweisen. Im übrigen *zeigte die Knochenfeinstruktur keine nennenswerten Veränderungen.* Der Verlauf der Knochenlamellen war nicht unterbrochen. Die kollagenen Kittlinien waren deutlich abgesetzt. Mit Vorbehalt darf man hieraus schliessen, dass *kein grober Mineralverlust* eingetreten ist. Auch

I LEY W., 1955 Probleme der Tympanoplastik 3 Mitteilung *Z Laryng Rhinol Otol* 34 719

MUSEDECK K., und FALK P., 1963 Uber knocherne Druckstrukturen in reponierten und homologen Steigbugeln und Knochenspanen *Arch Ohr Nas Kehlkopfheilk* 181 279

PORTMANN M., und CERESIA G., 1959 La reconstitution de l etrier par greffe osseuse *Rev Laryng* (Bord) 80 929

SCHUKNECHT H F., 1960 The metal prothesis for stapes ankylosis *Arch Otolaryng* (Chic) 71 287

SHEA J J 1958 Fenestration of the oval window *Ann Otol* 6 932

— 1962 Teflon piston operation for otosclerosis *Arch Otolaryng* (Chic) 6 516

UTECH H 1960 Bessere Endhorergebnisse bei der Tympanoplastik durch Veranderungen der Operationstechnik *Z Laryng Rhinol Otol* 39 367

WULLSTEIN H 1952 Funktionelle Operationen im Mittelohr mit Hilfe des freien Spalt lappen Transplantates *Arch Ohr Nas Kehlkopfheilk* 161 422

1960 Unsolved problems of tympanoplasty *Arch Otolaryng* (Chic) 71 588

— 1965 *Grundlagen und Methoden der Operationen zur Verbesserung des Gehörs* Unter Mitarbeit von W Kley O Bandtlow H G Schmitt und M E Wigand (In Vorbereitung)

WUSTROW F., 1954 Uber den Knochenfeinbau in Hammer und Amboss *Z Laryng Rhinol Otol* 33 06

ZANGEMEISTER H F., 1960 Stapesplastik zwecks Funktionserhaltung der Schalleitungs kette nach Eroffnung des ovalen Fensters bei nicht gelungener Mobilisation *Arch Ohr Nas Kehlkopfheilk* 1 6 19

ZOLLNER F., 1955 The principles of plastic surgery of the sound conducting apparatus *J Laryng* 69 637

— 195 Horverbessernde Operationen bei entzundlich bedingten Mittelohrveranderungen *Arch Ohr Nas Kehlkopfheilk* 171 1

— 1960 Technik der Formung einer Columella aus Knochen *Z Laryng Rhinol Otol* 39 536

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grosser Zahl vorhanden. Das Transplantat war von Epithel überzogen und in seiner Gesamtheit ausreichend ernährt.

Alle drei Knochenstücke waren also reizlos eingeheilt und erhielten über Bindegewebsbrücken eine ausreichende Ernährung. Die Knochenfeinstruktur war histologisch gut erhalten. Nur in einem Fall fanden sich 10 Jahre nach der Transplantation Umbauvorgänge, die aber die Kontinuität des Knochenstückes an keiner Stelle gefährdeten.

SUMMARY

Summarizing the results of our investigations we can say that the ossicle transplantations as well as the free bone grafts healed without any irritation and became nourished by even small connective tissue. Changes of the bone construction could not be observed in any case. A layer of epithelium covered the bone surfaces. Four out of nine autotransplanted ossicles showed lacunar and erosive changes of bone constructions the extension of which could not be brought into relation to the time passed after transplantation. There is some evidence that these changes had not been caused by the transplantation but by the previous otitis media.

Ossicles and bone pieces are very resistant when used as autotransplantates within the middle ear cavity or as a columella and to bridge defects of the ossicular chain. There is no danger of osteolysis by unsufficient alimentation because of adequate metabolism.

Therefore the problem of autotransplantation of ossicles and bone pieces is to get a good functional contact as well as to avoid adhesions with the surrounding tissue.

LITERATUR

BECK, Chl. und FRANZ, H. 1961. Das Verhalten ins Mittelohr implantierter auto- und homoioplastischer Knochenspäne im Tierexperiment. *Arch. Ohr.- Nas.- Kehlkopfheilk.* 179, 111.

BELLUCCI, R., und WOLFF, D. 1961. Tissue reaction following reconstruction of the oval window in experimental animals. III. Ossicular replacement of stapes. *Ann. Otol.* 70, 64.

ECKERT-MÖBIUS, A., 1926. Mikroskopische Untersuchungstechnik und Histologie des Gehörorgans. Denker-Kahler: *Handbuch der Hals-Nasen-Ohren-Heilkunde* 6, 211.

HALL, A., und RYTZNER, C. 1957. Stapedectomy and autotransplantation of ossicles. *Acta Otolaryng.* (Stockh.) 47, 318.

— 1959. Stapedektomie und Transplantation der Gehörknöchelchen. *Arch. Ohr.- Nas.- Kehlkopfheilk.* 175, 497.

— 1960. Vitality of autotransplanted ossicles. *Acta Otolaryng.* (Stockh.) Suppl. 158, 335.

— 1961. Autotransplantation of ossicles. *Arch. Otolaryng.* (Stockh.) [illegible] 22.

HERRMANN, H., 1959. Kann die Fussplattenplastik die Bogengangsfensterung ersetzen? *Arch. Ohr.- Nas.- Kehlkopfheilk.* 175, 502.

— 1960. Vergleichende Ergebnisse der Steigbügelmobilisierung und Fussplattenplastik. *Arch. Ohr.- Nas.- Kehlkopfheilk.* 176, 659.

HERRMANN, J., 1962. Erfahrungen mit frei transplantiertem Fascien-Bindegewebe des M. temporalis bei Tympanoplastik und Verkleinerung der Radikalhöhle. Knorpelbrücke vom Stapes zum unteren Trommelfellrand. *Z. Laryng. Rhinol. Otol.* 41, 141.

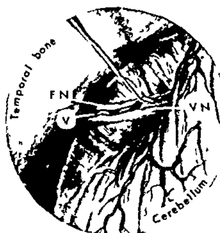


Fig 1



Fig 2

Fig 1 Operation field before section of vestibular nerve VN vestibular nerve FN facial nerve V vein

Fig 2 Operation field after section of vestibular nerve VN Vestibular nerve FN, facial nerve CN cochlear nerve V vein (sectioned)

Olivecrona (1943) has operated upon a total of 125 patients with Meniere s disease In the first 10 patients the whole of the acoustic nerve was divided In the remaining patients selective division of the vestibular branch was said to have been done In contrast to Dandy Olivecrona considers that it is possible to see a distinct demarcation between the vestibular and cochlear portions with the naked eye and that generally separation of the two branches presents no difficulty

Although this operative procedure can be considered safe quoad vitam it does not appear to have fulfilled the expectations attached to it This is specially true for the relatively poor results obtained with regard to hearing after the operation This may to some extent be due to the fact that earlier it has only been possible to operate under macroscopical visual control Following studies of the topographical anatomy of the internal auditory canal we have found that the nerves which enter the internal auditory canal however are surrounded by a thick pia mater and arachnoid membrane and cannot macroscopically be distinguished in a satisfactory manner After these studies we have carried out selective microscopic division of the vestibular nerve sparing the remaining nerves in 7 patients with unilateral Meniere s disease

Operative Technique

The skin is incised approximately 4 cm behind the external ear in a gentle curve about 10 cm in length The skin is stripped from the bone and the mastoid emissary located and coagulated with diathermy A triangular craniectomy with approximately 3 cm sides is made immediately above the mastoid foramen with the anterior border in immediate proximity to the posterior margin of the sigmoid sinus A T-shaped d[illegible] ion is employed with the upper shank

MICROSCOPIC INTRACRANIAL SECTION OF THE VESTIBULAR NERVE IN MÉNIÈRE'S DISEASE

A Preliminary Report

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Seven patients with unilateral Ménière's disease have been operated upon with microscopical intracranial selective section of the vestibular nerve. The operative technique is described. All the patients have complete preservation of hearing, taste and facial function postoperatively.

Of all the surgical methods employed in the treatment of Ménière's disease, intracranial section of the acoustic nerve probably has the oldest history.

The operation was suggested as early as 1871 by Charcot. The first surgical attempts at the eighth nerve were made by Krause in 1898 and by Wallace Marriage in 1904, but Frazier in 1912, following a suggestion of Mills (1908), was the first to divide the acoustic nerve intracranially.

The operation, however, was hazardous and actually did not come into general use before Dandy in 1928 reported 9 cases in which he had performed intracranial section of the acoustic nerve. The patients were followed up for periods ranging from 3 months to 3 years and during this period none of them had further attacks. In 1933 Dandy described a total of 30 cases in which this operative procedure was employed. It is true all these patients lost the little hearing they had, but this was not considered to be of any practical importance.

As early as 1928 Dandy suggested that it might be possible to divide only the vestibular portion of the acoustic nerve and spare the cochlear portion. He admitted that there is no macroscopic demarcation between the auditory and vestibular divisions of the acoustic nerve where it can be attacked surgically and that the exact limits of the vestibular branch only can be estimated. In 1933 he described a case in which approximately the anterior five-eighths of the nerve in cross section was divided, leaving the posterior three-eighths of the nerve intact. He assumed that the eighth nerve in cross section is equally divided between the auditory and vestibular divisions and that consequently the whole of the vestibular branch and in addition approximately one-eighth of the auditory branch should have been divided at the operation.

Around 1940–43 Dandy reported a further 20 cases in which only the vestibular branch was divided; all of them were relieved of their vertigo.

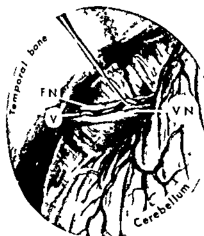




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running parallel with, and about 2 mm behind, the posterior border of the sigmoid sinus. The cerebellum is gently drawn aside with a dural retractor and its surface protected with cotton strips. If mannitol anaesthesia and hyperventilation are employed, there is such good space that the dural retractor is unnecessary. Following exposure of the internal auditory canal and the nerves passing through it, a continuous drainage is inserted immediately below the level of the nerves, in order to prevent the flow of cerebrospinal fluid from obscuring the field. The pia mater often lies as a fairly thick protective membrane over the nerves and must be carefully opened in order to permit a good view. The arachnoid membrane is then incised over the centre of the nerve parallel to the fibres. The demarcation between the vestibular and cochlear branch is then clearly seen. Through the microscopic lens this appears as a pale blue line running about midway between the two nerves. Occasionally small, fine veins are seen running along the outer surface of the vestibular nerve. These must be coagulated at both ends before dividing the nerve itself. With two needle-like instruments, specially made for the purpose, the vestibular nerve is then liberated from the cochlear nerve and also from its attachments to the intermediary nerve. With the small blunt hook the nerve is lifted up and divided with a fine dissecting knife. Before finishing the operation care is taken to ensure that the sheath of the vestibular nerve is completely empty and that the facial, cochlear and intermediary nerves are intact. The dura is then stitched with interrupted sutures, the bone defect covered with spongostan, and the skin flap sutured.

Results

All the seven patients operated upon with this method have complete preservation of hearing; two state that their hearing is somewhat better after the operation than before (about 10 dB). None of them have noticed any diminution of hearing following the operation. In three patients the tinnitus has completely disappeared while in four patients the noises in the ear persist unchanged. All of them have had surprisingly little discomfort from vestibular vertigo, which must be interpreted as due to extensive damage of the vestibular system by the primary disease. All the patients report that the preoperative pressure sensation in the ear has disappeared. No patient has exhibited any signs of damage to the intermediary nerve in the form om diminution of taste. In none of the patients has there been the slightest indication of injury to the facial nerve.

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